The Journal of Allergy

VOL. 10 JULY, 1939 NO. 5

Original Articles

ANTIGENIC STUDIES BY THE DALE TEST*

I. THE ANTIGENIC RELATIONSHIP OF CERTAIN POLLENS

STANLEY F. HAMPTON, M.D., ARTHUR STULL, PH.D., AND ROBERT A. COOKE, M.D., NEW YORK, N. Y.

THE purpose of this investigation was to study the antigenic relationship of the pollens of two related ragweeds, low *(Ambrosia elatior)* and giant *(Ambrosia trifida)*, and of three of the *Gramineae*, timothy *(Phleum pratense)*, orchard grass *(Dactylis glomerata)* and June grass *(Poa pratense)* as determined in the experimentally sensitized guinea pig, using the Dale test.[1]

Parker[2] reported the production of specific precipitins in rabbits and guinea pigs by a single injection of a suspension of ground giant ragweed pollen. The precipitins extended to a dilution of 1:50 in 2 of the 7 sera and were specific for giant ragweed pollen, there being no precipitins for low ragweed pollen. Cromwell and Moore,[3] however, with the precipitin test, and Armstrong and Harrison,[4] using the complement fixation test, found definite cross relationship of low and giant ragweed pollen, although the strength of the reaction was greater with the specific antigen.

Parker[5] first reported positive Dale reactions with pollen (giant ragweed) extract. Harrison and Armstrong[6] obtained gross anaphylaxis in two low ragweed sensitive guinea pigs by injections of giant ragweed pollen extract and in two giant ragweed sensitive guinea pigs by injection of low ragweed pollen extract. In addition, they report one Dale reaction, showing neutralization of a giant ragweed sensitive uterine muscle by low ragweed pollen extract. Walzer and Grove[7] found cross neutralization by the Dale test using low ragweed and giant ragweed sensitive guinea pigs.

*From the Department of Allergy, the Roosevelt Hospital, New York.

Presented before the Meeting of the Society for the Study of Asthma and Allied Conditions, April 29, 1939, Atlantic City, N. J.

Huber and Koessler,[8] from similar studies, stated that "the pollen from the two ambrosias gave small nonspecific reactions when tested against each other, and marked reactions when tested specifically." These authors do not present protocols but they show a reproduction of the tracing of a Dale reaction in which the uterine muscle was not tested for neutralization to the related ragweed pollen before the specific ragweed pollen was tested.

Adelsberger[9] has shown that guinea pigs sensitized to grass pollen gave positive Dale reactions.

Loeb[10] showed that guinea pigs sensitive to orchard grass pollen gave positive Dale reactions to the purified protein of orchard grass (ammonium sulfate precipitation) but not to the nonprotein filtrate.

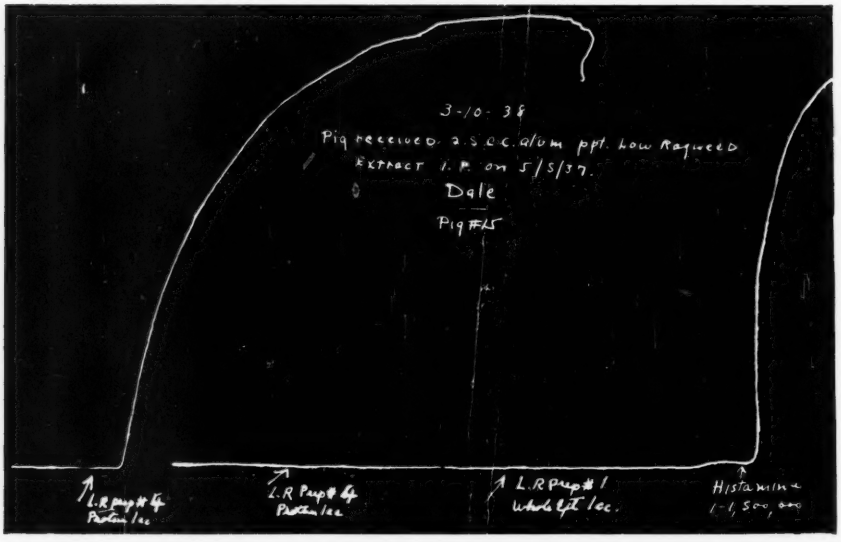


Fig. 1.—Guinea pig No. 15. See text.

EXPERIMENTAL PROCEDURE

Because it is more delicate and more easily interpreted than gross anaphylaxis, the Dale test was used for a quantitative study of the antigenic relationship of two related ragweed pollens (low and giant) and of three related grass pollens (timothy, orchard, and June).

The pollen extracts were prepared and standardized on the protein nitrogen content (1 unit = 0.00001 mg. protein nitrogen), as determined by phosphotungstic acid precipitation.[11]

In order to determine that this unit was a satisfactory basis for standardizing pollen extract in the later experiments, whole low ragweed pollen extract was compared with its purified protein prepared by repeated precipitations with saturated ammonium sulfate.

The following experiment was done:

Guinea pig No. 15, weighing 250 gm., was injected with 50,000 units of alum-precipitated low ragweed pollen extract on May 5, 1937. On March 10, 1938, the

guinea pig was killed and the uterus suspended in modified Tyrode's* solution. The purified protein (L. R. 4, Fig. 1) was first added to the bath in a 1 c.c. volume, containing 50,000 protein nitrogen units (0.50 mg. protein nitrogen). A typical contraction ensued, and after the bath was washed, a second addition of the purified protein was made in the same manner. The muscle failed to contract, signifying complete neutralization to the purified protein. After thorough washing of the bath, whole extract (L. R. 1, Fig. 1) was added in a 1 c.c. volume containing 50,000 protein nitrogen units (0.50 mg. protein nitrogen) and the muscle failed to contract.

Fig. 1 is a photograph of the tracing of this experiment, and is typical of the results obtained with duplicate procedures. The purified protein (L. R. 4) caused a contraction of the uterine muscle from guinea pigs sensitized with alum-precipitated low ragweed extract and completely neutralized the muscle to the whole extract (L. R. 1) of the same protein strength.

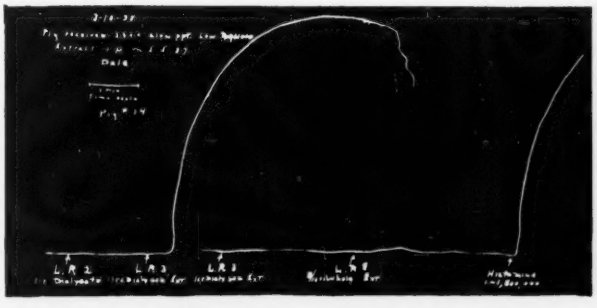
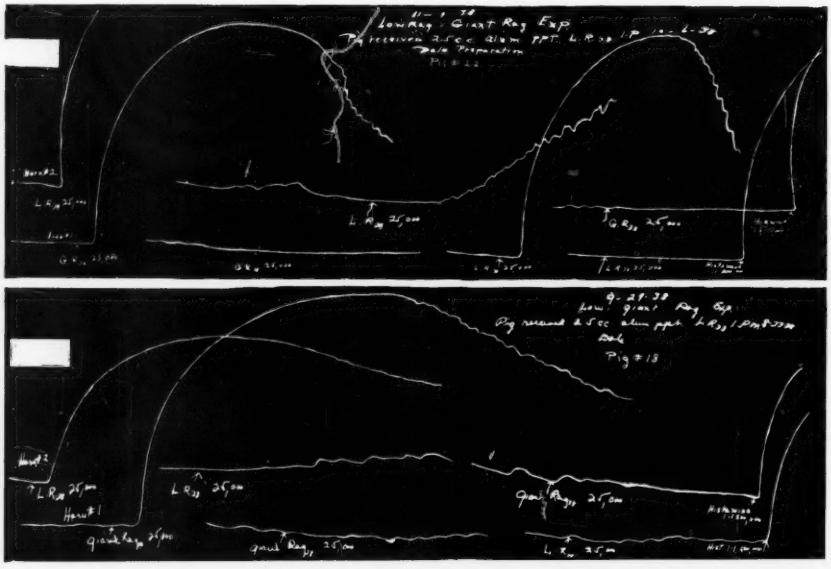


Fig. 2.—Guinea pig No. 14. See text.

Likewise, using equal protein strengths, dialyzed low ragweed pollen extract (L. R. 3, Fig. 2) produced a contraction and neutralized the uterine antibodies of guinea pig No. 14 sensitized by alum-precipitated low ragweed extract. Furthermore, the dialysate (L. R. 2, Fig. 2) that contained more total nitrogen (0.50 mg. per c.c.) than the dialyzed extract (0.40 mg. per c.c.) and only a negligible quantity of nitrogen precipitable by phosphotungstic acid (0.05 mg. per c.c.), failed to produce a contraction. This is analogous to the behavior of these same four preparations, the protein, the dialyzed extract, the dialysate, and the whole extract, in neutralizing the skin sensitizing substance found in the sera of patients with ragweed hay fever.[12]

Since the pollen protein, obtained by precipitation with ammonium sulfate, contained all of the antigen in whole pollen extract, the standardization of the latter was based on the protein content (protein nitrogen unit) for the quantitative studies to determine the antigenic relationship of the various pollens.

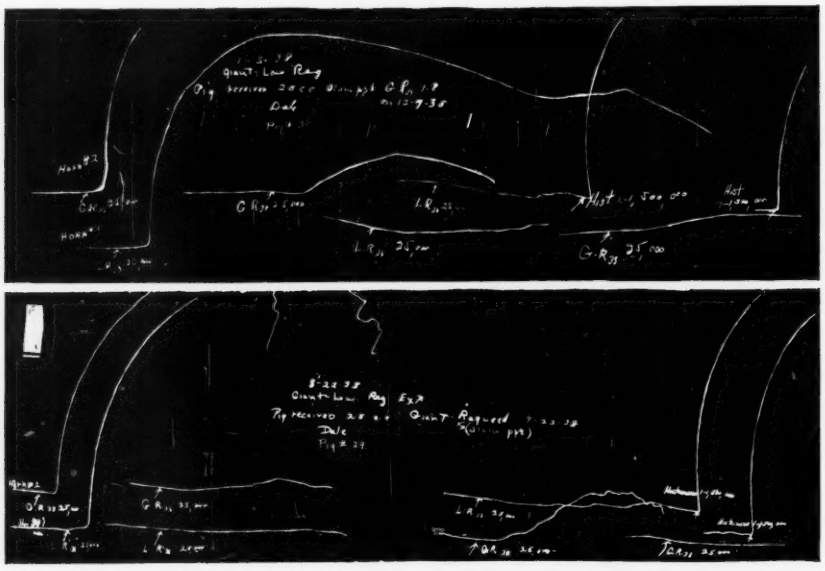
*Tyrode's solution modified to contain 0.025 gm. calcium chloride per liter. This modification reduced the spontaneous irritability of the uterine muscle which is so frequently encountered with the use of Tyrode's solution.



B.

A.

Fig. 3.—See Table II, guinea pig No. 18 (*A*) and guinea pig No. 22 (*B*).



A.

B.

Fig. 4.—See Table III, guinea pig No. 30 (*A*) and guinea pig No. 29 (*B*).

In the further observations, virgin female guinea pigs (250 to 300 gm.) were sensitized by a single intraperitoneal injection of 2.5 c.c. of washed alum-precipitated pollen extract containing 25,000 units per c.c. Harrison[13] found that this type of pollen extract readily sensitized guinea pigs. Table I shows the various antigens used in sensitization. After a lapse of at least three weeks, the guinea pigs were killed by exsanguination from the heart and the tests were performed. The

uterine horns were suspended in modified Tyrode's solution in a 150 c.c. bath at 37° C., and the contractions were recorded on the kymograph, as shown in Fig. 2. After each addition of pollen extract (not alum precipitated) to the bath, the uterine muscle was washed with 150 c.c. of modified Tyrode's solution before subsequent additions were made. At the completion of the experiment in each case, histamine 1:1,500,000 was added to show that the contractility was still present in that particular uterine horn.

In most instances, the dosage used in testing in the bath was 25,000 protein units. Preliminary experiments with varying dosage of extract, and the evidence presented by the purified protein experiments, indicated that an extract containing 25,000 units per c.c. was of satisfactory strength for these comparative studies.

TABLE I

GROUP	SENSITIZING ANTIGEN	NUMBER OF GUINEA PIGS INJECTED	NUMBER OF SENSITIVE GUINEA PIGS	RELATED ANTIGEN
Series A	Low ragweed	9	9	Giant ragweed
Series B	Giant ragweed	5	5	Low ragweed
Series C	Timothy grass	11	9	Orchard grass June grass
Series D	Orchard grass	10	8	Timothy grass
Series E	June grass	9	5	Timothy grass

The related pollen antigen (pollen extract other than the one used in sensitization, Table I) was first added to the bath. Recordings were made until the contraction reached a maximum and began to relax. After washing, when the horn was completely relaxed, a second addition of the related pollen antigen was made. In most instances, the horn failed to contract, signifying neutralization, although occasionally, subsequent addition of antigen was necessary. The specific pollen antigen (the pollen extract to which the pig was sensitized) was then added to the bath, always maintaining the same dosage. If there was a response, as manifested by a contraction, the specific pollen antigen was added until the muscle failed to contract. The second uterine horn, which had been kept in the modified Tyrode's solution during the testing of the first horn, was then suspended. In this instance, the specific antigen was first added to the bath. When repeated application had failed to produce contraction, signifying neutralization, the related antigen was tested. In order to control the time element, this order of testing was occasionally reversed.

RESULTS

Thirty-six guinea pigs out of the 44 used in this study were found sensitive by the Dale technique (Table I).

The shortest time between the sensitizing injection and the Dale test was twenty-one days, and the longest time was one hundred one days.

TABLE II

SERIES A. LOW RAGWEED POLLEN ANTIGEN

GUINEA PIG NO.	UTERINE HORN	DAYS BETWEEN SENSITIZING INJECTION AND DALE TEST	SENSITIZING ANTIGEN	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
17	1	38 days	L. R.*	G. R.†	25,000	++++
				G. R.	25,000	0
				L. R.	25,000	0
				L. R.	25,000	0
				H.‡		++++
	2			L. R.	25,000	++++
				L. R.	25,000	±
				G. R.	25,000	0
				H.		+++
18 See Fig. 3A	1	37 days	L. R.	G. R.	25,000	++++
				G. R.	25,000	0
				L. R.	25,000	0
				H.		++++
	2			L. R.	25,000	+++
				L. R.	25,000	0
				G. R.	25,000	0
				H.		+++
19	1	21 days	L. R.	G. R.	25,000	++++
				G. R.	25,000	0
				L. R.	25,000	++
				L. R.	25,000	0
				H.		++++
	2			L. R.	25,000	++++
				L. R.	25,000	0
				G. R.	25,000	0
				H.		+++
20	1	25 days	L. R.	G. R.	25,000	+++
				G. R.	25,000	0
				L. R.	25,000	0
				H.		+++
	2			L. R.	25,000	+++
				L. R.	25,000	0
				G. R.	25,000	0
				H.		+++
21	1	25 days	L. R.	G. R.	25,000	+++
				G. R.	25,000	0
				L. R.	25,000	+
				L. R.	25,000	0
				H.		+++
	2			L. R.	25,000	+++
				L. R.	25,000	0
				G. R.	25,000	0
				H.		++
22 See Fig. 3B	1	29 days	L. R.	G. R.	25,000	++++
				G. R.	25,000	0
				L. R.	25,000	++++
				L. R.	25,000	0
				H.		++++
	2			L. R.	25,000	+++
				L. R.	25,000	+
				G. R.	25,000	0
				H.		++++

*L. R. = Low ragweed.
†G. R. = Giant ragweed.
‡H. = Histamine 1:1,500,000.

TABLE II—CONT'D

GUINEA PIG NO.	UTERINE HORN	DAYS BETWEEN SENSITIZING INJECTION AND DALE TEST	SENSITIZING ANTIGEN	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
23	1	29 days	L. R.	G. R.	25,000	++++
				G. R.	25,000	0
				L. R.	25,000	0
				H.		++++
	2			L. R.	25,000	++++
				L. R.	25,000	0
				G. R.	25,000	0
				H.		++++
24	1	103 days	L. R.	G. R.	35,000	++++
				G. R.	35,000	0
				L. R.	35,000	+++
				L. R.	35,000	0
				H.		++
	2			L. R.	12,000	+++
				L. R.	12,000	±
				L. R.	12,000	0
				G. R.	12,000	0
				H.		+++
25	1	104 days	L. R.	G. R.	18,000	+++
				G. R.	18,000	0
				G. R.	18,000	0
				L. R.	18,000	0
				H.		+++
	2			L. R.	35,000	+++
				L. R.	35,000	++
				G. R.	35,000	0
				H.		+++

This variation apparently had no bearing upon the frequency with which the guinea pigs were found sensitive, nor upon the type of response in the Dale test.

A positive reaction was always obtained with the related antigen in all specifically sensitive guinea pigs (Tables II, III, IV, V, and VI). In spite of this, however, the study disclosed the fact that the specific and related antigens were not identical, as determined by the Dale test. This is shown in the critical analyses of the results summarized in the tables.

Series A: Low Ragweed Antigen. Giant ragweed pollen extract neutralized to low ragweed pollen extract in 5 experiments, but failed to neutralize in 4 of 9 experiments (see Fig. 3, *A, B;* Table II).

Series B: Giant Ragweed Antigen. Low ragweed pollen extract neutralized to giant ragweed pollen extract in 2 experiments and failed to neutralize in 4 of 6 (see Fig. 4, *A, B;* Table III). In one instance (guinea pig No. 27, Table III), both uterine horns were tested with low ragweed before testing with giant ragweed in order to duplicate the experiment, and the results obtained were essentially the same.

Series C: Timothy Grass Antigen. Orchard grass pollen extract neutralized to timothy grass pollen extract in 2 experiments and failed to

TABLE III

SERIES B. GIANT RAGWEED POLLEN ANTIGEN

GUINEA PIG NO.	UTERINE HORN	DAYS BETWEEN SENSITIZING INJECTION AND DALE TEST	SENSITIZING ANTIGEN	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
26	1	27 days	G. R.†	L. R.*	25,000	+
				L. R.	25,000	0
				G. R.	25,000	0
				H.‡		++
	2			G. R.	25,000	+++
				G. R.	25,000	0
				L. R.	25,000	0
				H.		+++
27	1	27 days	G. R.	L. R.	25,000	++
				L. R.	25,000	±
				L. R.	25,000	±
				L. R.	25,000	0
				G. R.	25,000	++
				G. R.	25,000	±
				H.		++
	2			L. R.	25,000	+
				L. R.	25,000	0
				G. R.	25,000	+
				G. R.	25,000	0
				H.		+
28	1	28 days	G. R.	L. R.	25,000	++
				L. R.	25,000	±
				L. R.	25,000	0
				G. R.	25,000	++
				G. R.	25,000	±
				G. R.	25,000	0
				H.		++
	2			Accidentally destroyed		
29 See Fig. 4*B*	1	31 days	G. R.	L. R.	25,000	++++
				L. R.	25,000	0
				G. R.	25,000	+
				G. R.	25,000	0
				H.		++++
	2			G. R.	25,000	++++
				G. R.	25,000	0
				L. R.	25,000	0
				H.		++++
30 See Fig. 4*A*	1	29 days	G. R.	L. R.	25,000	++++
				L. R.	25,000	0
				G. R.	25,000	0
				H.		++++
	2			G. R.	25,000	++++
				G. R.	25,000	+
				L. R.	25,000	0
				H.		++++

*L. R. = Low ragweed.
†G. R. = Giant ragweed.
‡H. = Histamine 1:1,500,000.

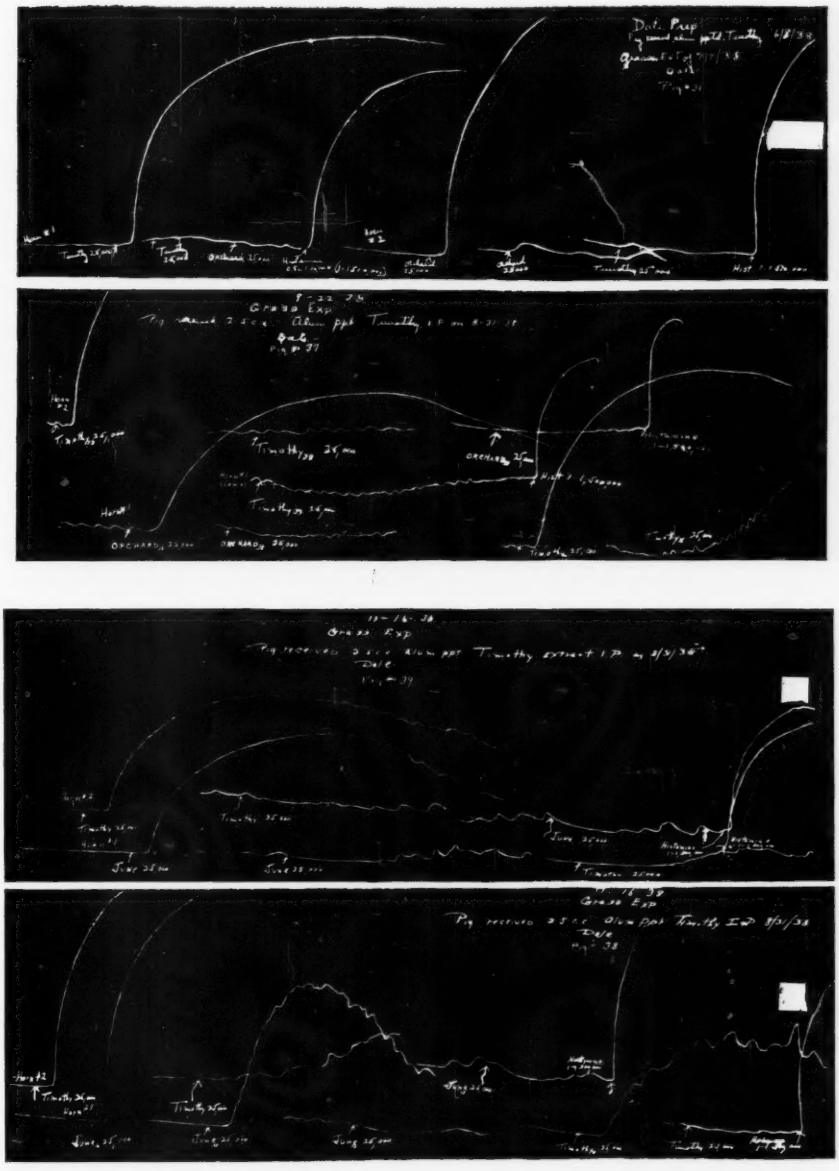


Fig. 5.—See Table IV, guinea pig No. 31 (*A*), guinea pig No. 37 (*B*), guinea pig No. 39 (*C*), and guinea pig No. 35 (*D*).

neutralize in 2 of 4. June grass pollen extract neutralized to timothy grass pollen extract in 4 experiments and failed to neutralize in 2 of 6 (see Fig. 5, *A, B, C, D;* Table IV). In one instance (guinea pig No. 33, Table IV), orchard and June grass pollen extract were tested as related antigens on the two respective uterine horns, and each antigen neutralized to timothy grass pollen extract.

Series D: Orchard Grass Antigen. Timothy grass pollen extract neutralized to orchard grass pollen extract in 3 experiments and failed to neutralize in 5 of 8 (see Fig. 6, *A, B;* Table V).

TABLE IV

SERIES C. TIMOTHY GRASS POLLEN ANTIGEN

GUINEA PIG NO.	UTERINE HORN	DAYS BETWEEN SENSITIZING INJECTION AND DALE TEST	SENSITIZING ANTIGEN	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
31 See Fig. 5A	2	33 days	Timothy	Orchard	25,000	++++
				Orchard	25,000	0
				Timothy	25,000	0
				H.*		+++
	1			Timothy	25,000	++++
				Timothy	25,000	0
				Orchard	25,000	0
				H.		++++
32	1	33 days	Timothy	June	25,000	+++
				June	25,000	0
				Timothy	25,000	0
				H.		+++
	2			Timothy	25,000	+++
				Timothy	25,000	0
				June	25,000	0
				H.		+++
33	1	37 days	Timothy	Orchard	25,000	++++
				Orchard	25,000	0
				Timothy	25,000	0
				H.		+++
	2			June	25,000	+++
				June	25,000	0
				Timothy	25,000	0
				H.		+++
34	2	69 days	Timothy	June	25,000	++
				June	25,000	0
				Timothy	25,000	0
				H.		++
	1			Timothy	25,000	+++
				Timothy	25,000	0
				June	25,000	0
				H.		++
35	1	79 days	Timothy	Orchard	25,000	++++
				Orchard	25,000	+
				Orchard	25,000	±
				Orchard	25,000	0
				Timothy	25,000	++
				Timothy	25,000	0
				H.		++++
	2			Timothy	25,000	++++
				Timothy	25,000	±
				Timothy	25,000	0
				Orchard	25,000	0
				H.		++++
36	1	25 days	Timothy	Timothy	25,000	0
				H.		++
	2			Timothy	25,000	0
				H.		++

*H. = Histamine 1:1,500,000.

TABLE IV—CONT'D

GUINEA PIG NO.	UTERINE HORN	DAYS BETWEEN SENSITIZING INJECTION AND DALE TEST	SENSITIZING ANTIGEN	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
37 See Fig. 5*B*	1	22 days	Timothy	Orchard	25,000	+++
				Orchard	25,000	0
				Timothy	25,000	+++
				Timothy	25,000	±
				Timothy	25,000	0
				H.		+++
	2			Timothy	25,000	+++
				Timothy	25,000	0
				Orchard	25,000	0
				H.		+++
38 See Fig. 5*D*	1	77 days	Timothy	June	25,000	++++
				June	25,000	++
				June	25,000	0
				Timothy	25,000	++
				Timothy	25,000	0
				H.		+++
	2			Timothy	25,000	++++
				Timothy	25,000	0
				June	25,000	0
				H.		++++
39 See Fig. 5*C*	1	77 days	Timothy	June	25,000	+++
				June	25,000	0
				Timothy	25,000	0
				H.*		+++
	2			Timothy	25,000	+++
				Timothy	25,000	0
				June	25,000	0
				H.		+++
40	1	77 days	Timothy	June	25,000	++++
				June	25,000	0
				Timothy	25,000	++++
				Timothy	25,000	0
				H.		++++
	2			Timothy	25,000	+++
				Timothy	25,000	+
				June	25,000	0
				H.		++
41	1	30 days	Timothy	Timothy	25,000	0
				H.		++
	2			Timothy	25,000	0
				H.		++

Series E: June Grass Antigen. Timothy grass pollen extract neutralized to June grass pollen extract in 5 experiments and failed to neutralize in none of 5 experiments (see Fig. 7; Table VI).

The related antigens neutralized to the specific antigen in 21 tests and failed to neutralize in 17 tests. The specific antigen always neutralized to the related antigen in the 32 tests performed.

In one experiment, marsh elder (*Iva ciliata*) pollen extract produced a positive Dale reaction in a low ragweed sensitive guinea pig uterus,

TABLE V

SERIES D. ORCHARD GRASS POLLEN ANTIGEN

GUINEA PIG NO.	UTERINE HORN	DAYS BETWEEN SENSITIZING INJECTION AND DALE TEST	SENSITIZING ANTIGEN	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
42	2	34 days	Orchard	Timothy	25,000	+++
				Timothy	25,000	0
				Orchard	25,000	++
				Orchard	25,000	0
				H.*		+++
	1			Orchard	25,000	+++
				Orchard	25,000	0
				Timothy	25,000	0
				H.		+++
43	2	35 days	Orchard	Timothy	25,000	+++
				Timothy	25,000	+
				Orchard	25,000	0
				H.		+++
	1			Orchard	25,000	++++
				Orchard	25,000	+++
				Orchard	25,000	0
				Timothy	25,000	0
				H.		+++
44	2	35 days	Orchard	Timothy	25,000	++++
				Timothy	25,000	0
				Orchard	25,000	0
				H.		+++
	1			Orchard	25,000	++++
				Orchard	25,000	0
				Timothy	25,000	0
				H.		++++
45	1	35 days	Orchard	Orchard	25,000	0
				H.		+++
	2			Orchard	25,000	0
				H.		+++
46	1	31 days	Orchard	Timothy	25,000	++
				Timothy	25,000	0
				Orchard	25,000	++
				Orchard	25,000	0
				H.		++
	2			Orchard	25,000	++
				Orchard	25,000	0
				Timothy	25,000	0
				H.		++
47	1	32 days	Orchard	Timothy	25,000	++
				Timothy	25,000	0
				Orchard	25,000	+
				Orchard	25,000	0
				H.		++
	2			Orchard	25,000	++
				Orchard	25,000	0
				Timothy	25,000	0
				H.		++

*Histamine 1:1,500,000.

TABLE V—CONT'D

GUINEA PIG NO.	UTERINE HORN	DAYS BETWEEN SENSITIZING INJECTION AND DALE TEST	SENSITIZING ANTIGEN	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
48 See Fig. 6*B*	1	33 days	Orchard	Timothy	25,000	+++
				Timothy	25,000	0
				Timothy	25,000	0
				Orchard	25,000	++
				Orchard	25,000	0
				Orchard	25,000	0
				H.		+++
	2			Orchard	25,000	+++
				Orchard	25,000	0
				Timothy	25,000	0
				H.		++
49 See Fig. 6*A*	1	26 days	Orchard	Timothy	25,000	++++
				Timothy	25,000	0
				Orchard	25,000	0
				H.		++++
	2			Orchard	25,000	+++
				Orchard	25,000	±
				Timothy	25,000	0
				H.		++
50	1	28 days	Orchard	Timothy	25,000	++
				Timothy	25,000	0
				Orchard	25,000	+
				Orchard	25,000	0
				H.		+
	2			Accidentally destroyed		
51	1	34 days	Orchard	Orchard	25,000	0
				H.		+++
	2			Orchard	25,000	0
				H.		+++

and although it neutralized the muscle to itself, it failed to neutralize it to low ragweed pollen extract. Bernstein[14] produced sensitivity with marsh elder pollen, shown by the presence of precipitins and the production of gross anaphylaxis.

CONCLUSIONS

Each sensitized uterine horn reacted to a related pollen antigen and was neutralized in 21 experiments. Since the related antigen did not neutralize the uterine muscle to the specific antigen in 17 experiments, but the specific antigen always neutralized the uterine muscle to the related antigen, it may be concluded that the extracts of the pollens botanically related showed a close antigenic relationship but were not identical.

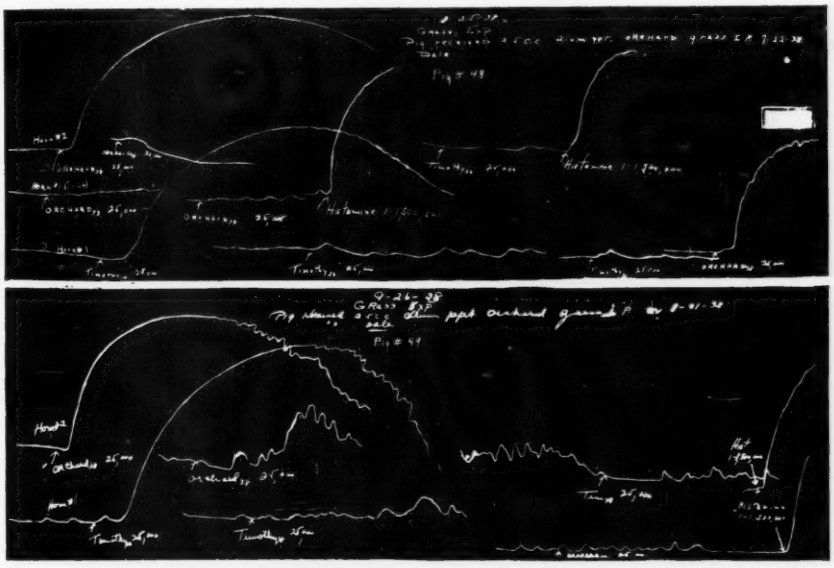
The variable results permit several interpretations and further studies are being made in the hope that an explanation of these differences may be found.

TABLE VI

SERIES E. JUNE GRASS POLLEN ANTIGEN

GUINEA PIG NO.	UTERINE HORN	DAYS BETWEEN SENSITIZING INJECTION AND DALE TEST	SENSITIZING ANTIGEN	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
52	1	38 days	June grass	June	25,000	0
				H.*		++
	2			June	25,000	0
				H.		++
53	1	35 days	June grass	Timothy	25,000	++++
				Timothy	25,000	0
				June	25,000	0
				H.		++++
	2			June	25,000	++++
				June	25,000	+
				June	25,000	0
				Timothy	25,000	0
				H.		++++
54	1	36 days	June grass	Timothy	25,000	++
				Timothy	25,000	0
				June	25,000	0
				H.		++
	2			June	25,000	++
				June	25,000	0
				Timothy	25,000	0
				H.		+
55	1	25 days	June grass	Timothy	25,000	+++
				Timothy	25,000	0
				June	25,000	0
				June	25,000	0
				H.		+++
	2			June	25,000	++
				June	25,000	0
				Timothy	25,000	0
				H.		++
56	1	25 days	June grass	June	25,000	0
				H.		+++
	2			June	25,000	0
				H.		+++
57	1	27 days	June grass	Timothy	25,000	++
				Timothy	25,000	0
				June	25,000	0
				H.		++
	2			June	25,000	+
				June	25,000	0
				Timothy	25,000	0
				H.		+
58	1	77 days	June grass	Timothy	25,000	++++
See Fig. 7				Timothy	25,000	0
				June	25,000	0
				H.		++++
	2			June	25,000	+++
				June	25,000	0
				Timothy	25,000	0
				H.		+++
59	1	35 days	June grass	June	25,000	0
				H.		+++
	2			June	25,000	0
				H.		+++
60	1	36 days	June grass	June	25,000	0
				H.		++++
	2			June	25,000	0
				H.		++++

*H. = Histamine 1:1,500,000.



B.

A.

Fig. 6.—See Table V, guinea pig No. 49 (*A*) and guinea pig No. 48 (*B*).

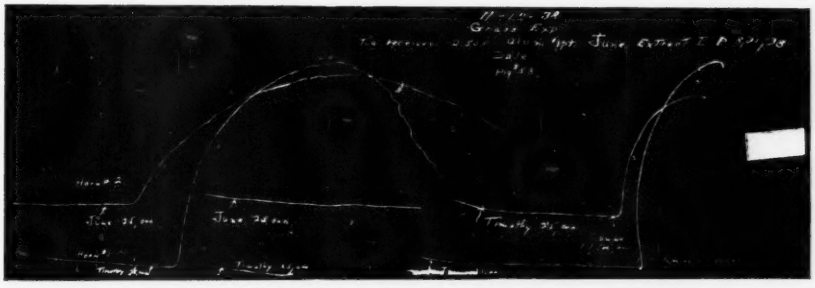


Fig. 7.—See Table VI, guinea pig No. 58.

The degree of muscular contraction varied in the guinea pigs, but, in general, it was found that the degree of contraction varied directly with the reaction of the muscle to the test solution of histamine hydrochloride (1:1,500,000).

SUMMARY

1. The protein fraction of low ragweed pollen extract produced muscular contraction and completely neutralized the uterine antibodies of guinea pigs sensitized by whole low ragweed pollen extract, as evidenced by the Dale test. Whereas, dialyzed low ragweed pollen extract also produced muscular contraction and neutralized the uterine antibodies to the whole extract, the dialysate completely failed to cause any contraction. The standardization of whole pollen extracts on the basis of their protein content was a measure of the reactive substance in whole pollen extract.

2. Specific pollen extract always neutralized to the related pollen extract.

3. A related pollen extract in every instance produced a contraction of the uterine horn sensitized by a specific pollen.

4. The related pollen extract neutralized to the specific in 21 instances and did not neutralize in 17 experiments.

5. These experiments indicate an antigenic relationship but not an identity of the pollens used in this study.

REFERENCES

1. Dale, H. H.: The Anaphylactic Reaction of Plain Muscle in the Guinea Pig, J. Pharmacol. **4**: 167, 1913.
2. Parker, Julia T.: The Production of Precipitins for Ragweed Pollen, J. Immunol. **9**: 515, 1924.
3. Cromwell, H. W., and Moore, M. B.: Studies on Pollen and Pollen Extracts. X. Antigenic Differences Between Short and Giant Ragweed Pollens, J. ALLERGY **4**: 347, 1933.
4. Armstrong, C., and Harrison, W. T.: A Study of Ragweed Pollen Extracts for Use in Treatment of Ragweed Pollen Hypersensitiveness, Pub. Health Rep. **39**: 2422, 1924.
5. Parker, Julia T.: The Antigenic Properties of Ragweed Pollen, Proc. Soc. Exper. Biol. & Med. **18**: 237, 1920.
6. Harrison, W. T., and Armstrong, C.: Some Experiments on the Antigenic Principles of Ragweed Pollen Extract (*Ambrosia elatior* and *Ambrosia trifida*), Pub. Health Rep. **39**: 1261, 1924.
7. Walzer, M., and Grove, E.: Studies in Specific Hypersensitiveness. XVI. On Antigens. A Comparative Study of the Antigenic Properties of Pollens, Egg-white, and Glue, in Guinea Pigs as Determined by the Intravenous and Dale Methods of Testing in Anaphylaxis, J. Immunol. **10**: 483, 1925.
8. Huber, H. L., and Koessler, K. K.: The Antigenic Properties of Pollens, Arch. Int. Med. **36**: 751, 1925.
9. Adelsberger, L.: Anaphylaxie und Atopie. III. Mitteilung. Anaphylaxieversuche mit Atopenen, Ztschr. f. Hyg. u. Infektionskr. **111**: 577, 1930.
10. Loeb, L. F.: Untersuchungen über die Chemische Natur der Allergene. IV. Biochem. Ztschr. **220**: 432, 1930.
11. Cooke, R. A., and Stull, A.: The Preparation and Standardization of Pollen Extracts for the Treatment of Hay Fever, J. ALLERGY **4**: 87, 1933.
12. Stull, A., and Sherman, W. B.: Further Studies on the Allergenic Activity of Protein and Nonprotein Nitrogen Fractions of Ragweed Pollen Extracts, J. ALLERGY **10**: 130, 1939.
13. Harrison, W. T.: Effect of Alum-Precipitated Ragweed Pollen Extract on Guinea Pigs, Pub. Health Rep. **49**: 462, 1934.
14. Bernstein, C.: Studies in Anaphylaxis With Pollen, J. Exper. Med. **61**: 149, 1935.

THE NATURE OF THE GRAIN DUST ANTIGEN*

Crossed Reactions to Grain Dusts and Smuts

Leonard H. Harris, M.D.
Elyria, Ohio

A SERIES of 13 patients allergic to grain dusts and to grain smuts has been reported.[1] Of these, all reacted strongly to wheat dust and oat dust, and all reacted, though usually not so strongly, to one or more smuts. Reagins to grain dusts and to grain smuts were transferable to the normal skin in every case attempted. The patients' symptoms of hay fever or of asthma could be readily reproduced in the untreated cases by the instillation of grain dust extracts or by the blowing of powdered smuts into the nose or trachea. These patients included farmers, farmers' children, 2 wheat mill chemists, and others who had experienced repeated attacks of hay fever or asthma after exposure to wheat dust or oat dust. This exposure had been experienced either during threshing time or while cleaning or handling the grains in barns or in grain mills. Several patients had observed that their allergy varied with the quality of the grain, and it was felt that wheat or oats that were "musty," but not necessarily smutty, caused most of their difficulty. The evidence, therefore, suggested grain dust and grain smut as definite etiology in these 13 patients. A possible antigenic relationship between grain dusts and grain smuts was at that time suspected because of the coincident allergy.

The purpose of this paper is to report on certain observations made relative to the nature of the antigen of wheat dust and wheat smuts and to the antigen of oat dust and oat smuts, and to report on certain in vivo and in vitro cross testing experiments done between wheat dust, smuts, and oat dust.

I. In vivo experiments

Following the technique outlined by Rackemann and Wagner,[2] serum was drawn from patients showing a high degree of sensitivity to wheat dust and oat dust. All these patients reacted strongly to most of the smuts, and 3 of them reacted to the common molds as well. The blood was refrigerated overnight and the serum then separated.

The recipients selected for passive transfer tests were normal with regard to personal and family history of allergy and negative to control tests. Serum was injected into sites 1½ inches apart, 0.1 c.c. intracutaneously into each site. After forty-eight hours, the sites were de-

*From the Cleveland City Hospital and the Elyria Memorial Hospital, Elyria.

sensitized with the selected grain dust or smut by daily injections until the sites were exhausted. The sites were then cross tested with the grain dust or smut to be studied. Other sites were used for direct transfers either before desensitization or after, to determine activity of sites.

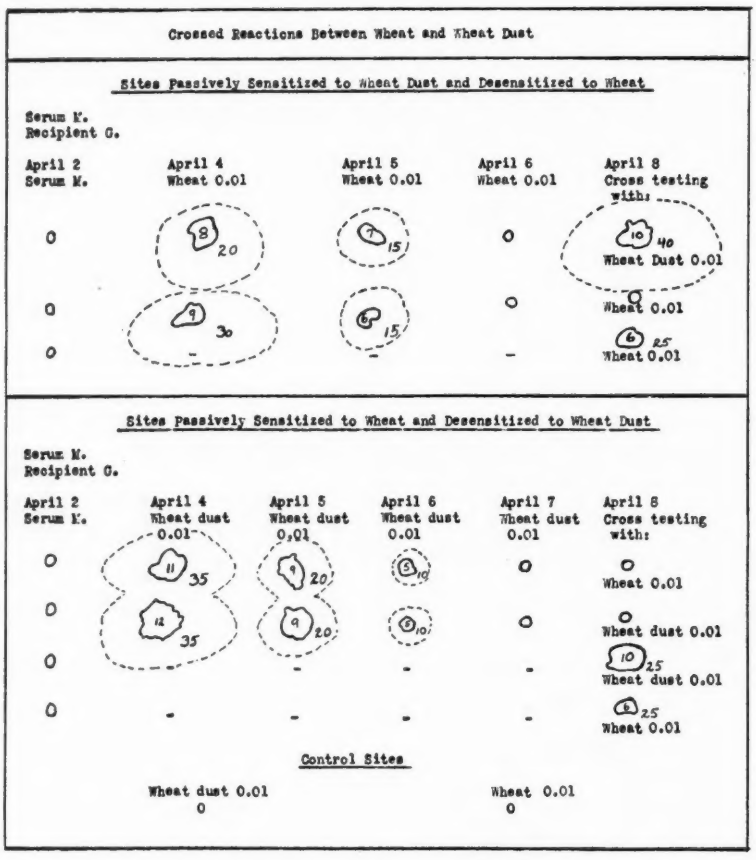


Fig. 1.—When sites were passively sensitized to wheat dust and then desensitized to wheat, these sites reacted to wheat dust. When sites were passively sensitized to wheat and then desensitized to wheat dust, these sites no longer reacted to wheat. The antigens of wheat and wheat dust are not identical. Figures in diagram equal millimeters.

Early in the work, attempts were made to neutralize a strong extract against a weaker one, for example, wheat dust 1:1000 dilution giving a four-plus reaction against *Ustilago tritici* 1:1000 dilution, giving a two-plus reaction. As might be expected, the neutralization was usually not reciprocal. Hence, subsequently, the work was repeated using extracts so diluted as to give, in the individual case, equal-sized reactions.

The results are reported by the above method of desensitization of a study of the interrelationship of wheat dust, oat dust, wheat, oat, and the following smuts: wheat smuts *(Tilletia tritici, Tilletia levis, Ustilago tritici),* oat smuts *(Ustilago avenae* and *levis)* (this was obtainable in combination only), and corn smut *(Ustilago zea).*

A. The Relationship of Wheat to Grain Dust Allergy.—Very early in this investigation, the question arose as to the relationship of the wheat dust antigen to wheat antigen. That it was not identical with the wheat antigen was indicated by several factors. First, most of the patients (66 per cent) did not react to wheat extract. Second, all of them could tolerate wheat when ingested. The first step appeared to be to determine whether wheat extract would mutually neutralize wheat dust extract. The same factors held equally well to oat dust and oats. Using extracts of equal nitrogen content, 0.01 per c.c., or using dilutions of equal potency (Fig. 1), it was found that when a site on a normal skin is passively sensitized to wheat dust and desensitized to wheat, the site will still react to wheat dust; but when desensitized to wheat dust, the site will no longer react to wheat. The antigens of wheat and wheat dust appear not to be identical. This was later confirmed by the in vitro method.

B. The Relationship of Molds to Grain Dust Allergy.—The notion that molds may play a part in grain dust allergy is by no means new. Blackley[8] in 1880 not only suspected molds in hay to cause hay fever, but actually isolated and identified a member of the *Chaetomium* group.

There were several factors which again suggested that a fungus, possibly a mold, was an etiologic factor in the production of grain dust. The first suggestion was found in the oft-repeated history given by some of these patients that grains with a moldy or "musty" odor were more apt to cause symptoms than clean wheat or oats. A few of these patients reacted quite strongly to a number of the common molds, such as *Alternaria, Helminthosporium, Aspergillus fumigatus, Mucor, Penicillium,* and *Hormodendrum. Chaetomium* reactions were very rarely obtained. Moreover, *Alternaria* and *Helminthosporium* spores have been found not infrequently in numerous samples of grain dust. Again, the distribution of *Alternaria* over the midwestern states coincides largely with wheat and oat growing districts, according to Durham.[3] The possible role of these molds playing a part in the production of grain dust has been investigated. Briefly, the present indications are that, although the spores of *Alternaria* and *Helminthosporium* may be present in grain dusts, they are not active in the production of the grain dust antigen. Nor is there any present evidence to indicate that any other mold is important in this connection.

Five of our 13 patients reacted strongly to molds as well as to grain dusts. Sera of 2 of these patients were therefore studied to determine if any common antigen could be discovered between the more common molds and the grain dusts. The results with serum I. H. (Fig. 2) was typical. Four sites were passively sensitized to *Alternaria* and *Helminthosporium* and then sensitized by daily injection with wheat dust and oat dust. After desensitization of the sites, it was found that *Alternaria* and *Helminthosporium* still reacted strongly.

TABLE I

COMPARISON OF SKIN-TEST POTENCY AND NITROGEN CONTENT OF WHEAT DUST SAMPLES STORED UNDER VARIOUS CONDITIONS

	A. SAMPLE OF WHEAT DUST IMMEDIATELY EXTRACTED	B. SAMPLE OF WHEAT DUST LEFT OPEN TO AIR, FILTERED THROUGH COTTON FOR FIVE MONTHS	C. SAMPLE OF WHEAT DUST LEFT OPEN TO AIR FOR FIVE MONTHS BEFORE EXTRACTION	D. SAMPLE OF WHEAT DUST AUTOCLAVED, SEALED, AND STORED FOR FIVE MONTHS BEFORE EXTRACTION	E. SAMPLE OF WHEAT DUST AUTOCLAVED, LEFT OPEN TO AIR BUT FILTERED THROUGH COTTON FOR FIVE MONTHS
Total nitrogen content in mg. per c.c.	0.675 mg. N per c.c.	0.631 mg. N per c.c.	0.535 mg. N per c.c.	0.297 mg. N per c.c.	0.257 mg. N per c.c.
Results of intracutaneous testing with wheat dust extracts using 0.01 mg. N per c.c.	0.01	0.01	0.01	0.01	0.01
Patient A. M.	++++	++++	+++	++	+++
Patient E. S.	+++	+++	++++	+++	++
Patient S. F.	++	++	++	+	+
Patient Ch. W.	++++	++	++	0	+
Patient Ca. W.	++	++	++	+	+

When samples of wheat dust were stored for five months either open to air or filtered through cotton, there was a slight loss of nitrogen and a slight loss of skin-test potency (columns B. and C.) when compared to a corresponding sample immediately extracted. Considerably greater loss was found when samples were autoclaved and then either sealed or left open to air through cotton (columns C. and D.).

Conversely, sites were also sensitized to oat dust and wheat dust (Fig. 2) and then exhausted by daily testing with *Alternaria* and *Helminthosporium*. When the sites were desensitized to these molds, they still reacted strongly to wheat dust and oat dust. It may, therefore, be concluded that there is no common antigen between these two molds and grain dust.

Efforts to culture molds from samples of grain dusts were fruitless because of the exuberant growths of a contaminating mold.* An extract was made from this mold, but no reactions were obtainable on any of these patients. Hence, less direct methods had to be resorted to.

In an effort to determine whether wheat dust contained an unidentified mold which might grow with aging, various wheat dust samples were allowed to stand for a period of five months under varying conditions, as suggested by Cohen's[4] work on house dust. A portion was immediately extracted. Other samples were stored open to air; open to air but filtered through cotton; autoclaved and sealed; autoclaved and then opened to air through cotton. After five months, 10 per cent extracts were made from the various samples, and the total nitrogen per cubic centimeter was determined for each. It was found that the nitrogen content and skin-test potency (Table I) had decreased slightly in the case of samples left open to air, or covered with cotton. Samples that

*Identified by S. M. Feinberg as a *Rhizopus*.

had been autoclaved, then stored for five months, either open to air or sealed tight, had lost half their nitrogen content, and on testing known patients the extracts appeared to have lost considerable skin-test potency. These facts then, failed to indicate that any living substance, such as molds, played any part in the production of grain dust.

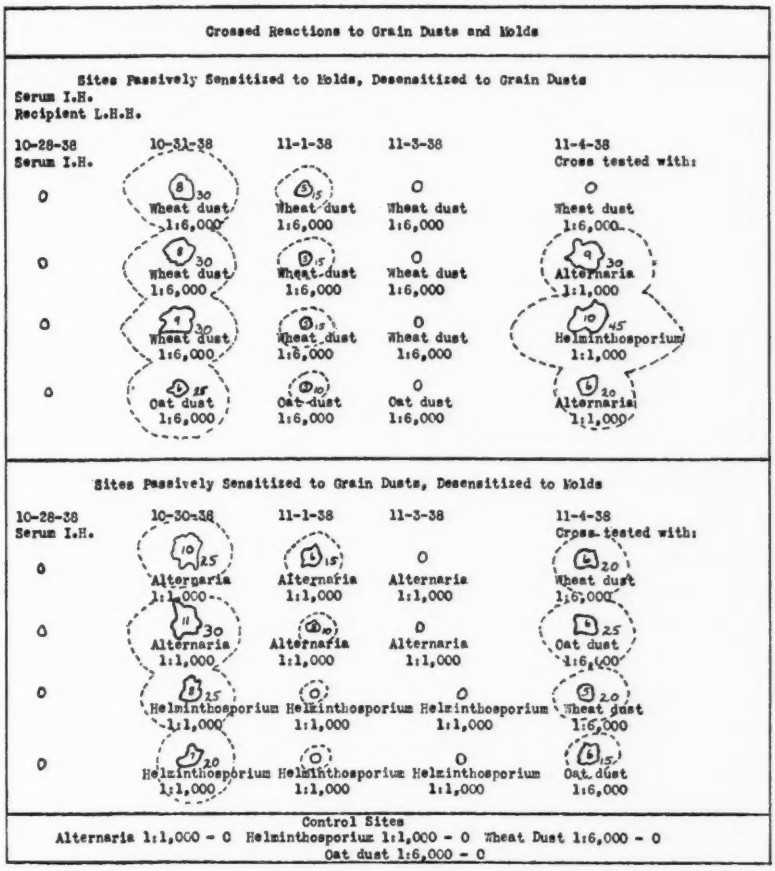


Fig. 2.—When sites were sensitized to the molds, *Alternaria*, and *Helminthosporium*, and were then desensitized to wheat dust and oat dust, the sites still reacted to these molds. When sites were sensitized to grain dusts and then desensitized to *Alternaria* and *Helminthosporium*, the sites still reacted to the grain dusts.

C. Crossed Reactions to Wheat Dust and Oat Dust.—In every case but one, it has been observed that sensitivity to oat dust is present where wheat dust sensitivity occurs. A common antigen was early suspected. In every instance desensitization of a passively sensitized site to wheat dust resulted in desensitization to oat dust as well (Fig. 3); conversely, sites desensitized to oat dust (not shown on figure) will not react to wheat dust, the reaction thus being reciprocal. The indication is that there is probably a common antigenic substance between wheat dust and oat dust, just as between wheat and oat extracts. One would expect then that allergy to these grain dusts would occur concomitantly, and this has

been a practical observation, with the one exception noted above. A second practical point is that treatment with wheat dust ought to protect against oat dust and vice versa. Convinced of this we have recently used wheat dust exclusively for treatment purposes.

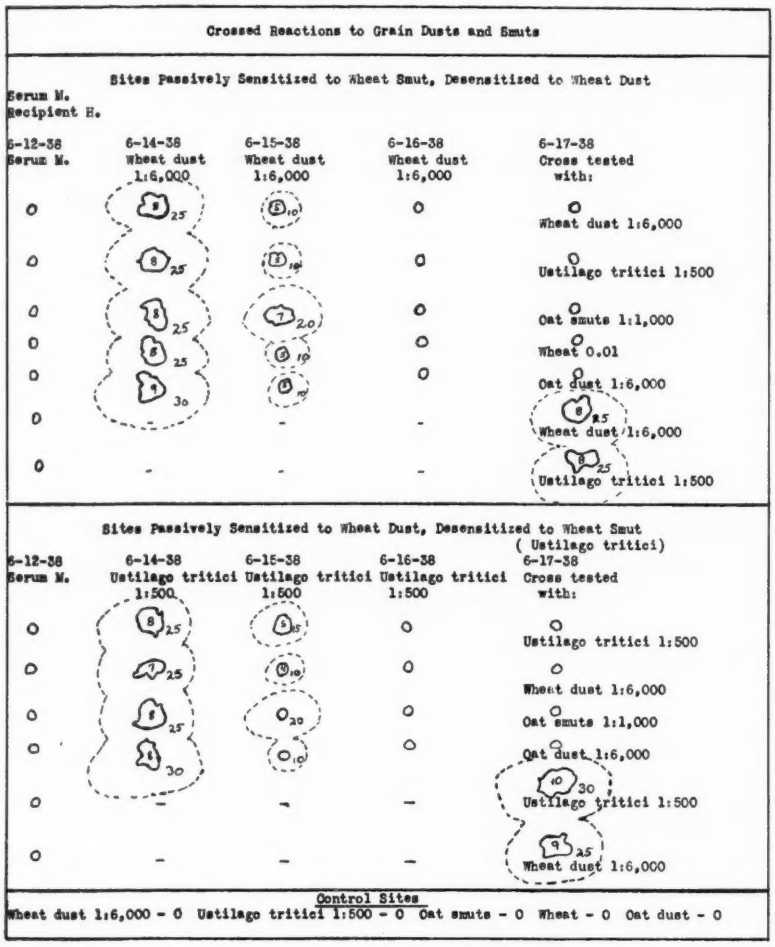

Crossed Reactions to Grain Dusts and Smuts
Sites Passively Sensitized to Wheat Smut, Desensitized to Wheat Dust
Serum M.
Recipient H.
6-12-38 Serum M.
6-14-38 Wheat dust 1:6,000
6-15-38 Wheat dust 1:6,000
6-16-38 Wheat dust 1:6,000
6-17-38 Cross tested with:
Wheat dust 1:6,000
Ustilago tritici 1:500
Oat smuts 1:1,000
Wheat 0.01
Oat dust 1:6,000
Wheat dust 1:6,000
Ustilago tritici 1:500
Sites Passively Sensitized to Wheat Dust, Desensitized to Wheat Smut (Ustilago tritici)
6-12-38 Serum M.
6-14-38 Ustilago tritici 1:500
6-15-38 Ustilago tritici 1:500
6-16-38 Ustilago tritici 1:500
6-17-38 Cross tested with:
Ustilago tritici 1:500
Wheat dust 1:6,000
Oat smuts 1:1,000
Oat dust 1:6,000
Ustilago tritici 1:500
Wheat dust 1:6,000
Control Sites
Wheat dust 1:6,000 - 0 Ustilago tritici 1:500 - 0 Oat smuts - 0 Wheat - 0 Oat dust - 0

Fig. 3.

Patient E. S. had been treated with wheat dust only, although clinically and on testing he was found to be hypersensitive to oat dust as well. The nasal test with oat dust was markedly positive. Two interesting observations were made on him. A maximum dosage of wheat dust extract 0.286 mg. nitrogen appeared to protect him against exposure not only to wheat dust but to oat dust as well. Convinced of its cross protection, on July 26, 1938, his usual wheat dust treatment was abruptly replaced by oat dust 0.213 mg. nitrogen with no unusual effects! In a second case of grain dust allergy, oat dust extract (nitrogen 0.14 mg.) was on one occasion substituted with no unusual effect for

wheat dust extract (nitrogen 0.14 mg.). These observations lead to the conclusion that a common antigenic substance occurs in wheat dust and oat dust, and that in treatment one extract will protect for the other.

D. The Relationship of Grain Smuts to Grain Dust.—The question as to the relationship between grain dusts and grain smuts is an interesting one. But here the question of relationship is moot and the answers are more difficult to determine. Certain factors have spoken in favor of the notion that there may be a relationship between wheat dust and wheat smuts *(Tilletia tritici* and *Ustilago tritici)* as well as between oat dust and oat smuts *(Ustilago avenae* and *levis)*. First, smut spores are to be found in practically any sample of grain dust. Roughly speaking these spores are more numerous in grains that have a "musty" odor. Second, spore counts have been found to be particularly high during the threshing season,[5, 6] and it is during this season that most discomfort is experienced by grain dust sensitive patients. Third, a striking coincidental allergy to grain dusts and grain smuts has been observed in 13 patients who reacted to grain dust.[1] Fourth, there appears to be some immunologic relationship between grain dusts and grain smuts. The evidence here presented appears to indicate a common factor between wheat dust and a wheat smut, *Ustilago tritici* (Fig. 3).

However, there are two technical difficulties in working with smuts. First, they cannot be grown on artificial media in the laboratory. Second, the difficulty in separating the smut from the host always raises the practical question: "How much wheat or wheat dust is there in an extract made from smut balls?" Probably the contamination is slight, but present nonetheless.

Several sites were passively sensitized to wheat smut (Fig. 3) and then desensitized to wheat dust. The sites then failed to react to *Ustilago tritici.* Using serum which contained reagins for *Tilletia tritici,* it was similarly found that sites, passively sensitized to wheat smuts and desensitized to wheat dust, failed to react to *Tilletia tritici.* In both instances oat smuts failed to react on desensitized sites. That the sites were still active was indicated by the fact that *Alternaria* and *Helminthosporium* strongly reacted after desensitization to wheat dust.

Sites were then passively sensitized to wheat dust and desensitized to *Ustilago tritici* (Fig. 3). When wheat dust was injected into these desensitized sites, no reaction was obtained; hence wheat dust and wheat smut *(Ustilago tritici)* were found to be reciprocally neutralized. No reactions were obtained when sites desensitized to *Ustilago tritici* were cross tested with corn smut *(Ustilago zea),* oat smuts *(Ustilago avenae* and *levis),* and wheat bunt *(Tilletia tritici)* (Fig. 4); but when the desensitization tests were reversed, reactions were frequently obtained. Therefore, cross neutralization tests between various smuts did not appear to be complete or reciprocal (Fig. 4).

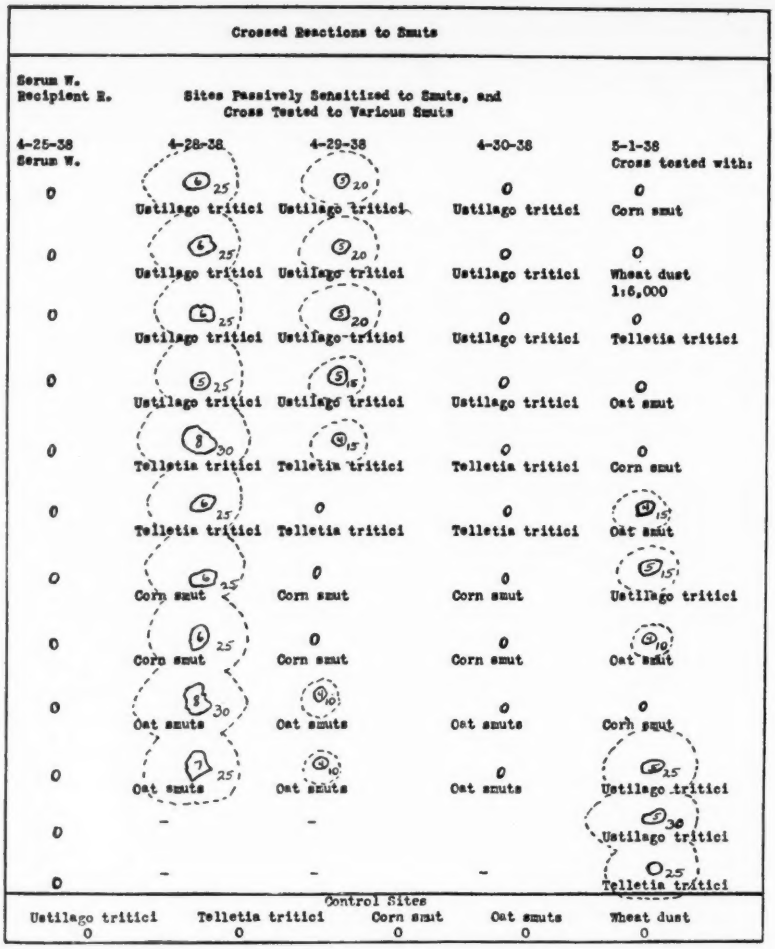


Fig. 4.

Sites tested with:	Serum incubated with wheat dust 0.1 mg N.	Serum incubated with oat dust 0.1 mg N.	Serum incubated with Ustilago tritici 1:33	Serum incubated with wheat 0.1 mg N.	Serum incubated with oat smuts Ustilago Avenae & levis 1:33	Serum incubated with Saline
1. Wheat dust 0.01	0	0	0			
2. Oat dust 0.01	0	0	0		0	
3. Wheat 0.01	0	0	0	0		
4. Ustilago tritici 1:500	0	0	0	0	0	
5. Oat smuts 1:1,000	0	0	0	0	0	

Control Sites

Wheat dust 0.01 - 0
Oat dust 0.01 - 0
Ustilago tritici 1:500 - 0
Ustilago levis & avenae- 0 1:1,000
Wheat - 0

Fig. 5.—In vitro neutralization of serum reagins and cross testing with grain dusts and smuts.

Patient A. M.
Recipient L. H. H.
Serum drawn 2/25/39
Serum injected 3/2/39
Cross testing 3/5/39

II. IN VITRO EXPERIMENT

To further investigate this apparent close immunologic relationship between wheat dust, oat dust, and the various smuts, most of the preceding cross testing work was repeated by the in vitro method. The purpose here was to neutralize the serum reagins in the test tube, inject the neutralized serum into various sites on a normal individual, and then proceed with cross testing. The sera of two patients (A. M. and T. R.) were used on four recipients. Both sera contained reagins to wheat dust, oat dust, wheat, wheat smut *(Ustilago tritici)* and oat smuts *(Ustilago levis* and *avenae),* and the results were similar with both sera.

Equal parts (1 c.c.) of serum and the corresponding antigens were incubated at 37° C. for four hours and kept in a refrigerator overnight as follows:

1. One cubic centimeter undiluted serum incubated with 1 cubic centimeter wheat dust (0.1 mg. N/c.c.).
2. One cubic centimeter undiluted serum incubated with 1 cubic centimeter oat dust (0.1 mg. N/c.c.).
3. One cubic centimeter undiluted serum incubated with 1 cubic centimeter *Ustilago tritici* (3 per cent).
4. One cubic centimeter undiluted serum incubated with 1 cubic centimeter wheat extract (0.1 mg. N/c.c.).
5. One cubic centimeter undiluted serum incubated with 1 cubic centimeter oat smuts (3 per cent *Ustilago avenae* and *levis*).
6. One cubic centimeter undiluted serum incubated with 1 cubic centimeter physiologic saline.

The following day 0.1 c.c. of each mixture was injected into 36 sites each on two nonreacting normal subjects. After seventy-two hours, the sites were tested with results as shown in Fig. 5.

Sites that were injected with serum neutralized with wheat dust failed to react to oat dust, wheat, or smuts. The same was found to be true of serum neutralized with oat dust. This is interpreted as indicating reciprocal neutralization between wheat dust, oat dust, and their respective smuts. When sites were passively sensitized, with serum neutralized with wheat extract, sites still reacted to wheat dust and to oat dust, indicating that neutralization was not mutually reciprocal between wheat and either grain dust. Sites that had been passively sensitized with serum incubated with *Ustilago tritici* gave negative results when tested with strong reacting wheat dust and oat dust. Moreover, wheat or oat smuts did not react. This is interpreted as indicating a probable common antigen between wheat dust and wheat smut, *Ustilago tritici.* When sites were passively sensitized with serum incubated with oat smuts, only wheat dust reacted but oat dust and *Ustilago tritici* failed to do so. The neutralization was here unilateral.

Then sites were passively sensitized with serum incubated with physiologic saline and then tested. Reactions were obtained for wheat dust,

oat dust, *Ustilago tritici, Ustilago levis* and *avenae,* and to wheat, indicating the activity of the sites. The control tests on the normal skin were all negative.

CONCLUSIONS

1. Wheat dust and oat dust will neutralize each other reciprocally in vivo and in vitro. Oat and wheat dust extracts of equal nitrogen content may be used interchangeably for testing or treatment.

2. Wheat dust will neutralize wheat, but wheat will not desensitize to wheat dust.

3. Wheat dust and *Ustilago tritici* will neutralize each other reciprocally in vivo and in vitro and probably have a common antigen.

4. The same is likely true for oat dust and oat smuts, *Ustilago levis* and *avenae.*

5. Molds in general, according to the evidence presented, are not related antigenically to grain dust.

6. Specifically, no evidence can be found to indicate any relationship between *Alternaria, Helminthosporium,* or *Rhizopus* in the grain dust antigens.

7. Cross testing between various smuts would indicate that while there is some cross neutralization, these smuts do not all have a common factor.

8. The close relationship between the antigen of wheat dust and wheat smut is indicated, and the suggestion is made of the possibility that wheat smut acting on wheat *may* produce the wheat dust antigen.

REFERENCES

1. Harris, L. H.: Allergy to Grain Dusts and Grain Smuts, J. ALLERGY **10**: 327, 1939.
2. Rackemann, Francis M., and Wagner, H. C.: The Desensitization of Skin Sites Passively Sensitized With Serum of Patients With Hay Fever. Crossed Reactions of Different Pollens. The Variation in the Recipient, J. ALLERGY **7**: 319, 1936.
3. Durham, O. C.: Incidence of Air-Borne Fungus Spores. II. Hormodendrum, Alternaria and Rust Spores, J. ALLERGY **10**: 40, 1938.
4. Cohen, M. B., Nelson, T., and Reinarz, B. H.: The Nature of House Dust Antigen, J. ALLERGY **6**: 517, 1935.
5. Durham, O. C.: Personal communication.
6. Wittich, F. W.: Personal communication.
7. Wagner, H. C., and Rackemann, F. M.: Crossed Reactions to Household Dusts, J. ALLERGY **8**: 537, 1937.
8. Blackley, C. H.: Hayfever, Its Causes, Treatment, and Effective Prevention, Experimental Researches, London, 1880, Baillière, Tindall and Cox.

Molds used in this study were grown from cultures supplied and identified by Dr. S. M. Feinberg. Various grain smut extracts were obtained from the same source; others, made by the Arlington Chemical Co., were first obtained through the generosity of Dr. F. W. Wittich. Later the *Ustilago* smuts were obtained from the United States Department of Agriculture and extracted in our laboratory.

STUDIES WITH ANTIGENS

II. The Use of Comparative Skin Reaction Curves in the Determination of the Skin Reacting Potency of House Dust Extracts

B. G. Efron, M.D., New Orleans, La., and
Ralph I. Dorfman, Ph.D., New Haven, Conn.

IN ADDITION to the potency of any extract, the identity of the person on whom it is tested and the location of the test on the skin have been recognized for a long time as factors affecting the size of skin reactions. In a recent communication we showed that the skin reaction curve to serial dilutions of a house dust extract was a discontinuous one. It was thus demonstrated that in a given subject, a given size skin reaction may be produced by concentrations of the extract which vary tremendously, so that equal size skin reactions may denote a very wide range of difference in extract potency. The curves showed also an overwhelming tendency toward similar sized reactions in the upper ranges of concentration of the extract, although equal sized reactions occurred in all ranges of concentration.

Since direct skin tests for the determination of potency of extracts are in constant use, and since our findings indicated that comparative skin tests must be accepted with extreme caution, we investigated the possibility of developing a more satisfactory method of assay.

Comparative skin reaction curves to serial dilutions of extracts offered a possible solution of the problem of estimating comparative potency of extracts. In the absence of pertinent factors affecting parallel comparative reaction curves, this procedure seemed valid.

Serial dilutions of a biologically active house dust extract were made. To each one part of dust extract was added the following parts of Coca's solution, and the resulting dilutions labeled as indicated in Table I.

Scratch tests were made on the forearms along the vertical axis in parallel rows, one row on the radial, and the other on the ulnar side. The scratches were about ⅜ inch long, about 1 inch apart. No more than four pairs of scratches were made on each forearm in adults, and not more than three pairs in children. Analogous dilutions were always placed on parallel scratches at the same level. The order with which the concentrations were tested were always from the more concentrated to the less. Since only a few dilutions could be applied at one visit, subsequent tests were made on further visits. Tests at such times were usually started at least with the last concentration used on the previous visit; at times, they were started with one or two concentrations above

TABLE I

DILUTION	DUST EXTRACT	COCA'S SOLUTION PARTS	PERCENTAGE CONCENTRATION AS USED IN GRAPHS
D	1	0	100
$\frac{D}{1.50}$	1	0.50	66.66
$\frac{D}{2}$	1	1.0	50
$\frac{D}{3}$	1	2.0	33.33
$\frac{D}{4}$	1	3.0	25
$\frac{D}{5}$	1	4.0	20
$\frac{D}{6}$	1	5.0	16.66
$\frac{D}{7}$	1	6.0	14.33
$\frac{D}{8}$	1	7.0	12.50
$\frac{D}{9}$	1	8.0	11.11
$\frac{D}{10}$	1	9.0	10
$\frac{D}{11}$	1	10.0	9
$\frac{D}{12}$	1	11.0	8.5
$\frac{D}{13}$	1	12.0	7.7
$\frac{D}{14}$	1	13.0	7
$\frac{D}{15}$	1	14.0	6.66
$\frac{D}{18}$	1	17.0	5.5
$\frac{D}{20}$	1	19.0	5
$\frac{D}{25}$	1	24.0	4
$\frac{D}{30}$	1	29.0	3.33
$\frac{D}{40}$	1	39.0	2.50
$\frac{D}{50}$	1	49.0	2
$\frac{D}{60}$	1	59.0	1.66
$\frac{D}{80}$	1	79.0	1.25
$\frac{D}{100}$	1	99.0	1

the last one tested. This was done intentionally in order to minimize as far as possible the known differences in the reactivity of the skin at the elbow and the wrist. Many concentrations were tried several times on one patient; in many instances, the whole series of concentrations were retested. All the skin tests were performed and read by only one of us (B. G. E.).

The reactions were recorded as marked plus (M+), marked (M), marked moderate (Mm), moderate (m), moderate slight (MS), plus minus slight (±S), and plus minus or negative (± or 0). This system was chosen in order that slight variations in reaction size could be noted.

The skin reaction curves were represented by means of graphs. Representative ones were selected for publication, since it was impractical to present all the curves completed. None of the unpublished graphs differed essentially from those presented. The serial concentrations of the test solutions used were expressed in percentages of the original dust extract taken as 100 per cent and plotted on the abscissa of the graph, while the reaction sizes were classified according to the above described scheme and plotted on the ordinate.

RESULTS

A. Comparative Skin Reaction Curves With the Same Extract.—Comparative skin reaction curves with the same dust extract were completed on 20 patients. Figs. 1* through 5 represent the results of this study.

Theoretically, parallel tests, made simultaneously with serial concentrations of an extract, should produce similar or equal sized reactions, provided, of course, there were no extraneous factors affecting the reactivity of the parallel skin sites. Under the actual conditions of the test, with care and technical precision, parallel scratches of identical size and depth may be practically attained in most instances, but in a certain number of instances, this is not accomplished. Size and depth of the scratches are important factors influencing the size of reactions.

Location of the skin site from the elbow to the wrist, would not be a pertinent factor in comparative skin reaction curves, since each pair of tests was placed on the same level on the forearm. Location of the skin site would affect both tests to the same degree.

The subjective factor, i.e., the classification of reactions from day to day, a source of experimental error, would be operative toward each test to the same degree.

The variation in skin sensitivity of the patient from day to day, if present, would affect both curves to the same degree. This leaves but one other element to consider, and that is, whether or not there is a difference in the reactivity of the skin between the radial and ulnar side of the forearm. Examination of Figs. 1 through 5 showed such differences. In Fig. 2, at 50 per cent and 33.33 per cent concentrations, the sizes of

*Solid circles, solid line represent reactions on the radial side of forearm. Hollow circles, broken line represent reactions on the ulnar side of forearm.

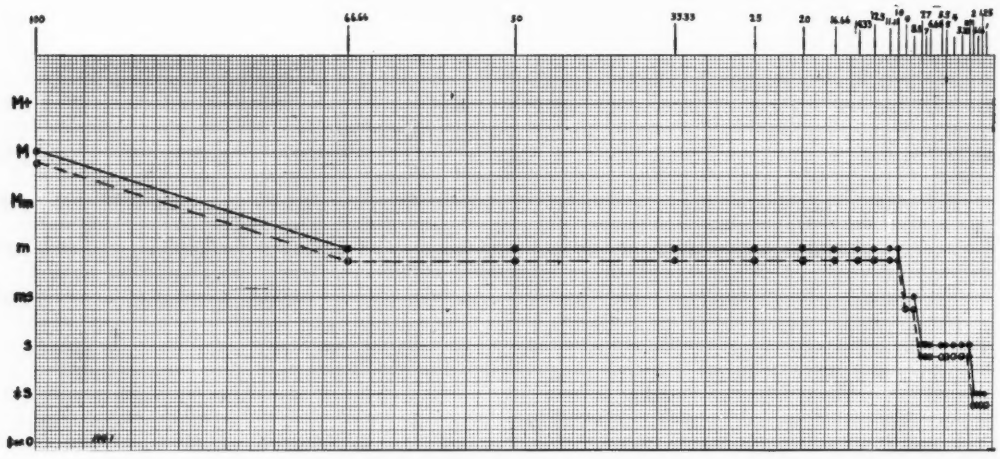


Fig. 1.—Readings were made on 25 different concentrations to produce these curves. Parallel skin reaction curves were obtained.

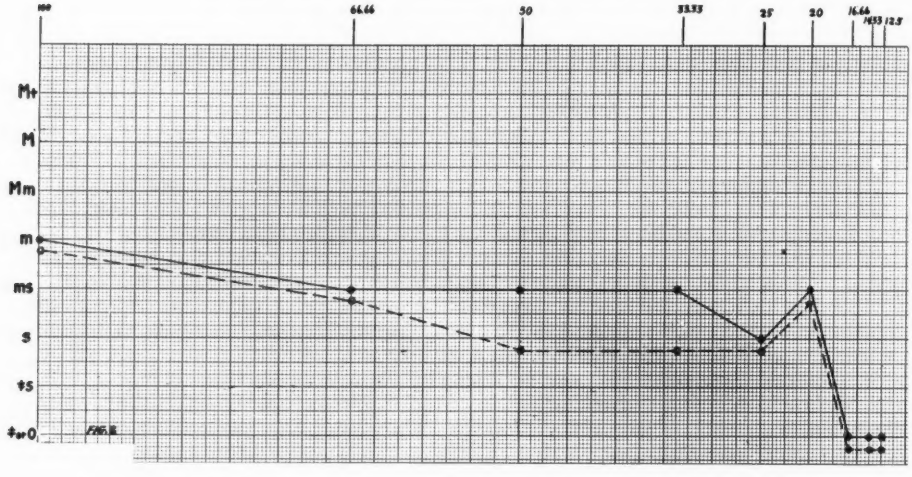


Fig. 2.—Readings were made on 18 different extract concentrations to produce the curves; the ulnar reactions were smaller at 50 per cent and 33.33 per cent concentrations; at all other concentrations reactions were similar.

reactions were smaller at the ulnar site than at the radial. Fig. 3 showed crossing of the curves; at 66.66 per cent concentration, the radial reaction predominated, but at 50 per cent concentration, the ulnar was larger, while at 33.33 per cent concentration, the reactions of both were equal. At 12.50 per cent concentration, the ulnar reaction was larger, but at 11.11 per cent, 10 per cent, 9.09 per cent, and 8.50 per cent, the radial was larger.

Figs. 4 and 5 represent comparative reaction curves made on the same forearm of the same patient on different occasions. In Fig. 4 the radial sites were distinctly larger than the ulnar, except at 100 per cent concentration, where the two were similar; but in Fig. 5 equal sized

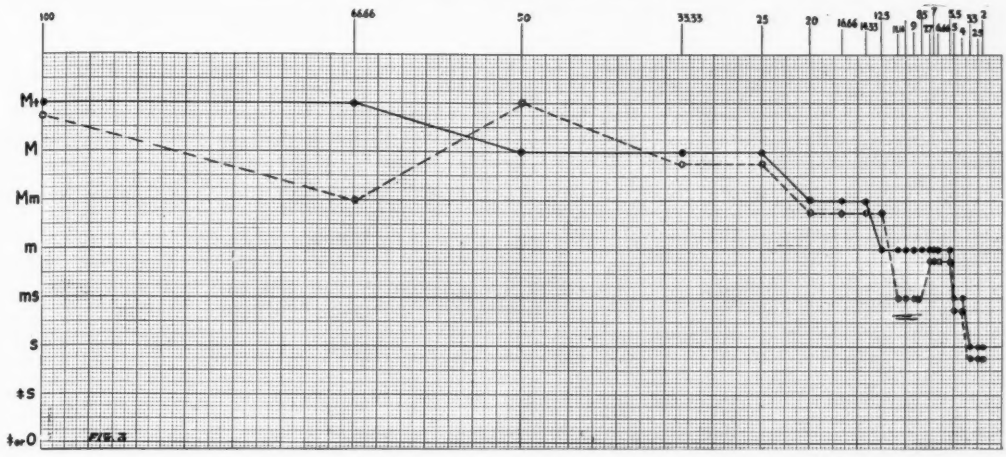


Fig. 3.—Twenty-two different concentrations were tested to produce these curves. The reactions were equal at 100 per cent concentration; the radial reaction was larger than the ulnar at 66.66 per cent concentration, but the ulnar reaction was larger than the radial at 50 per cent concentration; the curve is parallel through 33.33 per cent, 25 per cent, 20 per cent, 16.66 per cent, and 14.3 per cent concentrations. At 12.5 per cent concentration, the ulnar reaction is larger than the radial, but at 11 per cent, 10 per cent, 9 per cent, and 8.5 per cent concentrations, the radial reactions are larger than the ulnar. From 7 per cent concentration through 2 per cent concentration, the reactions were again equal.

The "crossing" of the curves is indicative of differences due to the experimental error of the test. Note that despite occasional differences in reaction size with different concentrations of extracts, there was practical parallelism of the curves.

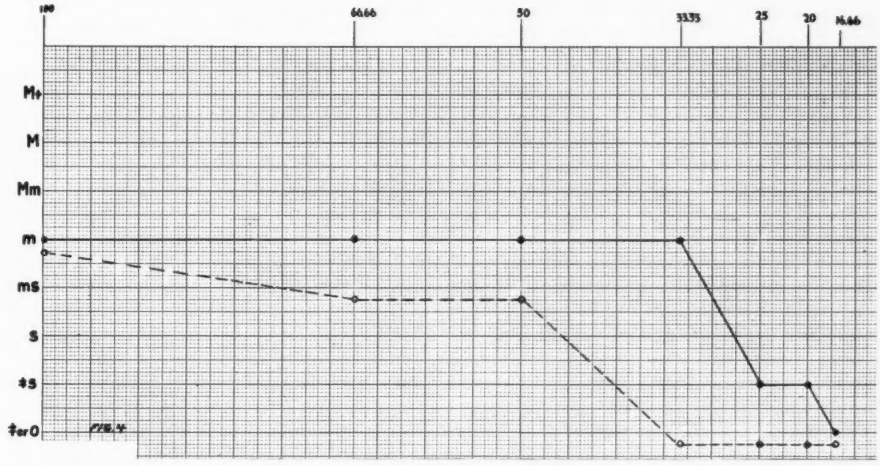


Fig. 4.—The curves were completed with but seven different concentrations; except at concentrations 100 per cent and 16.66 per cent, the radial reactions are distinctly larger than the ulnar. The curves are not parallel (see Fig. 7).

reactions occurred at 100 per cent concentration and at 66.66 per cent concentration. The ulnar reaction was larger than the radial at 50 per cent concentration; at 33.33 per cent and 25 per cent, the radial reaction sizes were larger than the ulnar.

These observations indicated that whatever differences in reaction size were present on the radial or ulnar side of the forearm, they were not due to inherent differences in the reactivity of the skin sites, but

were more probably dependent upon the error produced by slight differences in the size and depth of the scratches.

The number of concentrations necessary to be tested to complete a skin reaction curve varied greatly. From this standpoint patients could be divided into (a) those in whom a comparatively large number of serial concentrations were required to complete the curve, i.e., 10 or more, and (b) those in whom a small number were necessary.

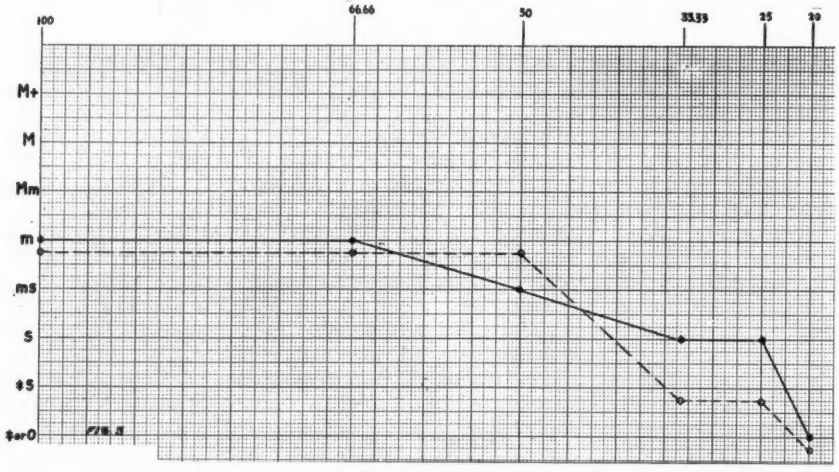


Fig. 5.—Note the greater parallelism of the curves with these readings. The reactions at 100 per cent concentration and at 66.66 per cent concentrations were equal in size; at 50 per cent concentration, the ulnar reaction was greater than the radial, but at 33.33 per cent and at 25 per cent concentrations, the radial reactions were larger than the ulnar.

The greater the number of observations, the less was the percentage of experimental error. This observation was illustrated by Figs. 1, 2, and 3, representing cases belonging to the "a" group of patients. Here it was noted that differences in skin reactions at analogous serial concentrations did not materially affect the equality of the comparative curves. It was also noted in this group that there was a definite tendency for differences at analogous serial concentrations to be compensated for by reverse differences in reaction sizes, at other portions of the curve. For example, in Fig. 3, at 66.66 per cent concentration the size of the radial reaction was larger than that of the ulnar, whereas at concentration 50 per cent, the radial reaction size was smaller.

In the "b" group of cases, on the other hand, differences in reaction size between the radial and ulnar series had a pronounced effect on the equality of the curves. In Fig. 4 differences in reaction size at four analogous serial concentrations produced complete nonequality of the curves. In Fig. 5, differences with two analogous serial concentrations affected markedly the character of the comparative curves. The same observation was made in Fig. 2.

In order then to reduce the effect on comparative curves of differences in reactions due to experimental error, it is advisable to use curves for comparative tests that contain the reactions produced by at least eight to ten serial concentrations.

Differences in skin reactions caused by dust extracts and measured by means of comparative skin reaction curves to serial concentrations show: (1) The skin reaction curve to serial concentrations of extracts is a discontinuous one; equal sized reactions occur for wide ranges of concentration of extract. (2) Reactions of greater size denote greater potency, provided that differences due to the size and depth of the scratches, location of the test sites, and diurnal variation in the skin sensitivity are taken into account.

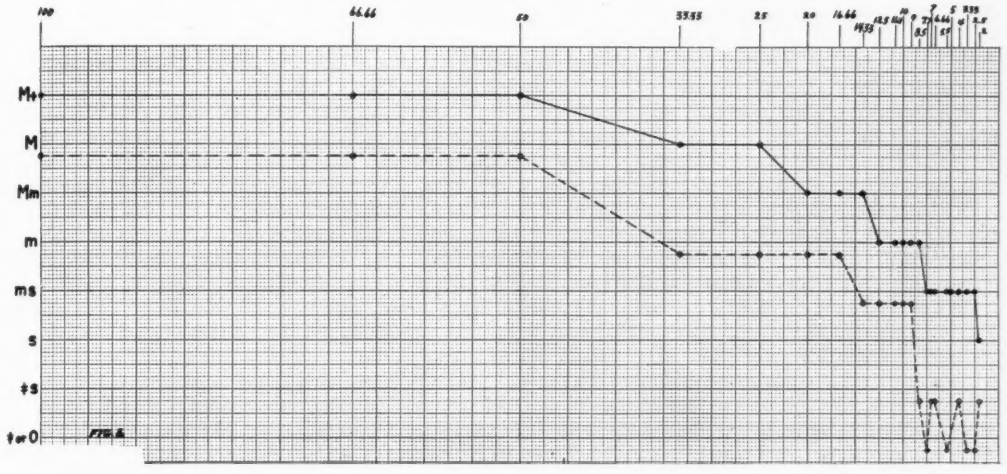


Fig. 6.—The R-4-37 extract produced definitely larger reactions for the same concentrations than did R-5-36. Equal size reactions did not occur at any serial concentration. No serial concentration in the R-5-36 curve produced a reaction larger than a serial concentration in the R-4-37 curve. The R-4-37 curve was definitely higher. Solid circles, solid line = R-4-37. Hollow circles, hollow line = R-5-36.

B. Comparative Skin Reaction Curves With Dust Extracts.—Serial dilutions of two dusts (R-5-36 and R-4-37*) were made on the same day, by the technique previously described. Comparative skin reaction curves were completed with these two preparations on 16 patients. Figs. 6, 7, and 8 indicate the results obtained. Representative graphs were selected for publication. In this series there were 8 patients belonging to the "a" group, and 8 to the "b" group.

Of the 16 patients tested, all the R-4-37 curves were "higher" than the R-5-36 curves; none of the curves were equal and none of the R-5-36 curves were higher than the R-4-37 curves. This indicated that R-4-37 had greater skin reacting potency than did R-5-36.

*Preparations R-5-36 and R-4-37 represented dust extracts that were prepared by redissolving the residues obtained after ultrafiltration of crude extracts. The dusts were extracted with dextrose solution.

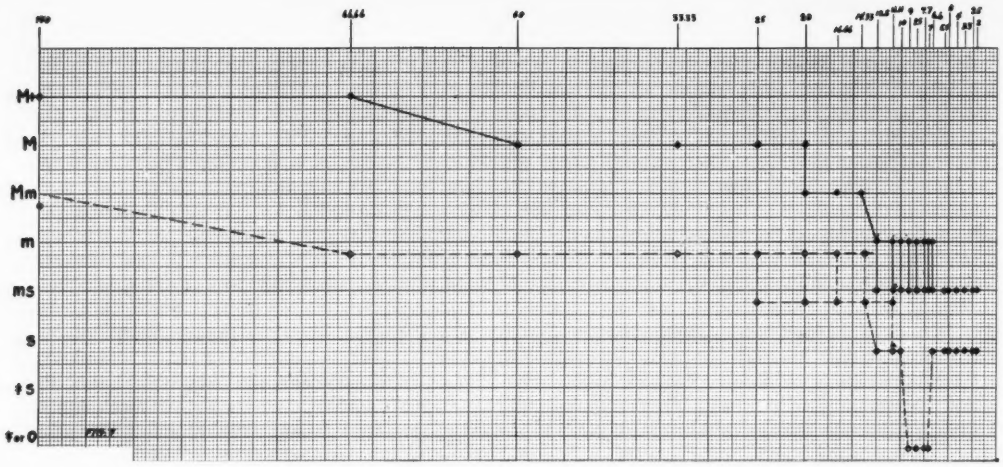


Fig. 7.—Twenty-two serial concentrations were tested. The R-4-37 series produced larger reactions at all concentrations tested. No equal sized reactions were obtained at any serial concentration compared. The R-5-36 series produced no larger reaction at any serial concentration. The R-4-36 curve was definitely higher. Note the 11 per cent concentration reactions; at test (1) R-4-37 produced an M reaction, while the R-5-36 produced an MS; when test with this concentration was repeated, (2) R-4-37 produced an MS, and R-4-36 an S reaction.

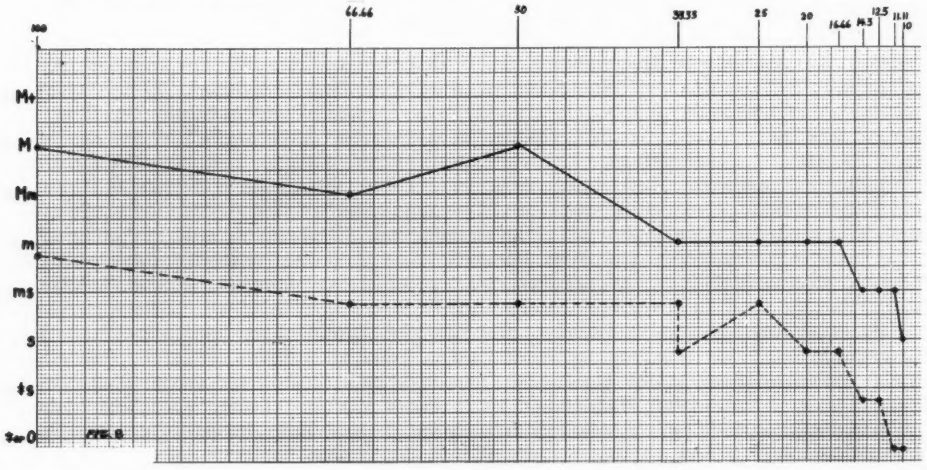


Fig. 8.—Eleven serial dilutions were compared. The R-4-37 series produced larger reactions at all serial concentrations. The R-4-37 curve was definitely higher.

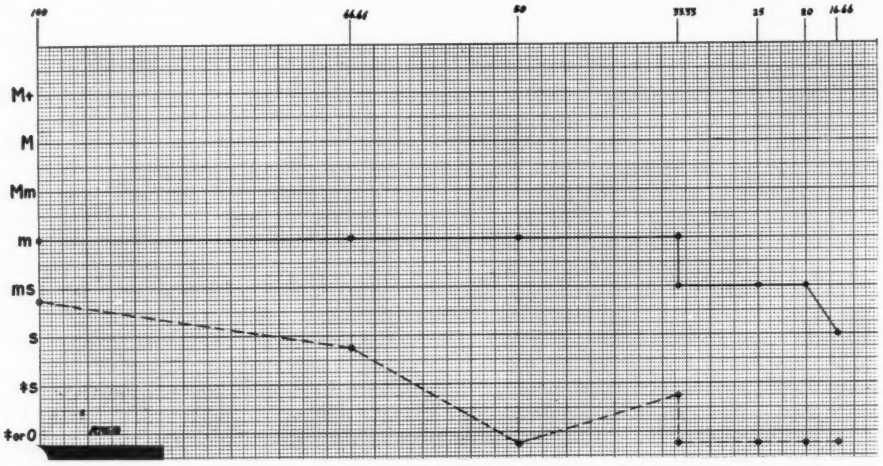


Fig. 9.—Seven serial concentrations were compared. The R-4-37 series produced larger reactions at all serial concentrations tested. The R-4-37 curve was definitely "higher."

Figs. 9, 10, and 11 show the results of comparative skin reaction tests obtained with a third dust (D-1-37 and R-4-37). Comparative skin reaction curves were completed on 15 patients. In this series 8 patients belonged to the "a" group, and 7 to the "b" group.

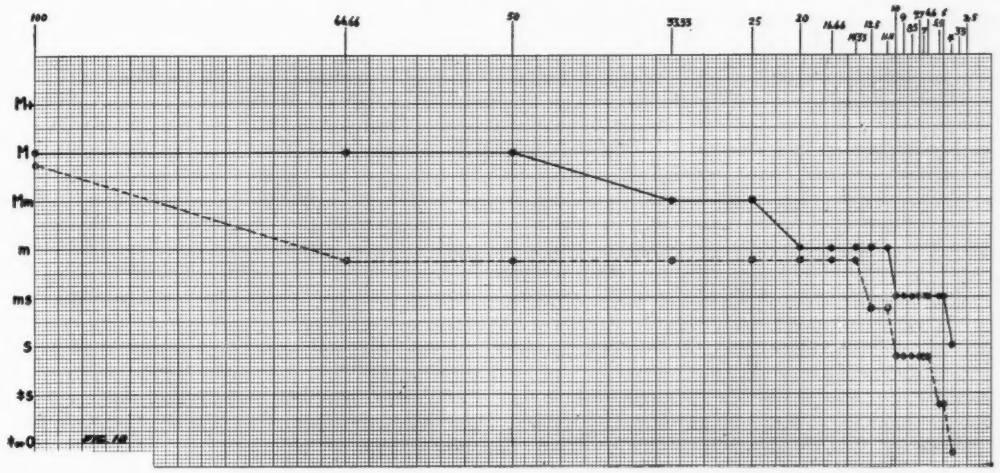


Fig. 10.—Twenty-one serial concentrations were compared. The R-4-37 series and the D-1-37 series produced equal sized reactions at four serial concentrations; the R-4-37 series produced larger reactions at seventeen serial concentrations; the D-1-37 series produced no larger reactions. The R-4-37 curve was definitely higher.

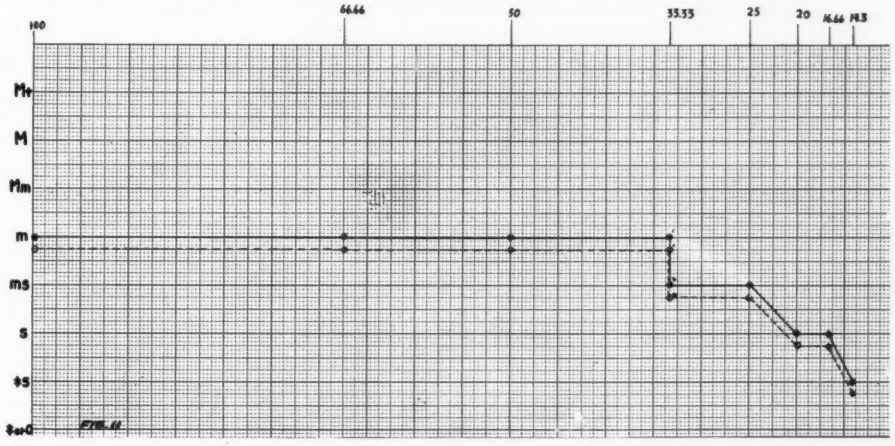


Fig. 11.—Eight serial concentrations tested. Equal size of reactions for both series were present throughout the curve.

Of the "a" group: In 8 patients the R-4-37 curves were higher than the D-1-37, in no instance was the R-4-37 curve equal to D-1-37, and in no instance was the R-4-37 curve lower than the D-1-37 curve.

Of the "b" group: In 1 patient the R-4-37 curve was higher than the D-1-37, in 6 patients the R-4-37 curves were equal to the D-1-37 curves, and in no case was R-4-37 curve lower than the D-1-37.

This indicated that dust extract R-4-37 had greater skin reacting potency. Since no comparative skin reaction curves were done between

preparation D-1-37 and R-5-36 extracts, it was not certainly established which of these two was more potent. However, from a study of the comparative curves of each with extract R-4-37, it is very likely that extract D-1-37 was the stronger of the two. Clinically, extract R-5-36 could be substituted for extract D-1-37 without reactions; but in each of 3 patients where preparation D-1-37 was substituted for extract R-5-36, systemic reactions occurred.

CONCLUSIONS

1. Skin reaction curves to house dust extracts are discontinuous, with plateaus of reaction size for wide ranges of potency (concentration).

2. Comparative skin reaction curves can determine qualitative differences in the skin reacting potency of house dust extracts.

REFERENCE

1. Dorfman, R. I., and Efron, B. G.: Studies With Antigens. I. The Skin Reaction Curve Obtained With Serial Dilutions of Extracts, J. ALLERGY **9**: 464, 1938.

COMBINED ORAL AND SUBCUTANEOUS TREATMENT FOR RAGWEED POLLINOSIS*

McKinley London, M.D.
Cleveland, Ohio

IN 1927 Black,[1] a hay fever sufferer, ingested 34.5 c.c. of a 5 per cent mixed ragweed pollen extract, over a period of seven days. He skin tested himself with blood serum drawn at the end of this period, and obtained a positive reaction which equaled that of a 1:20,000 ragweed extract. Passive transfer experiment showed a comparable reaction; this method also demonstrated ragweed principle in the urine.

Because his mucous membranes showed an increased tolerance to ragweed pollen after the ingestion of ragweed extract, he treated 73 ragweed sensitive patients orally the next year. Treatment was practically coseasonal. The dosage was 10 minims of a 5 per cent ragweed extract and increased by 10 minims at each administration, three times a day, until the dose reached 60 minims three times a day. This dose was maintained twice weekly. Results, while not as good as with subcutaneous therapy, were gratifying.

McGrew[2] reported excellent results in 33 patients taking 1 to 10 drops three times a day of a 1 per cent solution, averaging 4 drops three times a day.

Stier and Hollister[3] tried this method on 347 patients suffering from hay fever due to pollen other than ragweed. While the largest dose was 21 drops of a 1:100 extract daily, most of them took much lower quantities. These investigators reported results as good as those generally reported for subcutaneous therapy.

Rockwell[4] treated patients, most of whom were sensitive to ragweed and some to the grasses, with preseasonal oral therapy. He reached a level of 120,000 Noon units and maintained that dose several times weekly during the season. He reported satisfactory results in 63.2 per cent and no relief in 24.1 per cent.

The preceding reports encouraged us in the belief that results with subcutaneous therapy could be enhanced by coincidental oral administration.

CLINICAL

Combined oral and subcutaneous therapy was tried on 23 patients in 1938 who, in the previous year, were treated by subcutaneous therapy alone. The combined treatment was also applied to 19 patients who

*From the Allergy Clinic, St. Luke's Hospital, Cleveland.
Read before the Cleveland Allergy Society, May 23, 1939.

had not been treated the previous year. The schedule of progressively increasing quantities of extract injected was maintained in all patients, ignoring the factor of oral administration. Oral therapy was begun during the last week in July and continued until mid-August. The initial dose was 2 minims of a 5 per cent extract of mixed ragweed, well diluted with water, and administered three times a day after meals. The dose was raised by 2 minims at each administration semiweekly, so that most patients were taking 10 minims three times a day by mid-August and had consumed about 1 ounce in total dosage. Many patients voluntarily took much larger doses. Constitutional reactions in patients so treated were exceedingly few and no more than in patients treated subcutaneously alone. Foods giving positive tests were eliminated; dust injections were given where dust was thought to be a factor.

Table I records details for each patient treated in 1937 and 1938.

TABLE I

COMPARISON OF PATIENTS TREATED BY SUBCUTANEOUS THERAPY IN 1937 AND BY COMBINED THERAPY IN 1938

PATIENT	MAX. DOSE 1937 MG. N	PERCENTAGE IMPROVEMENT 1937	MAX. DOSE 1938 MG. N	DAILY ORAL DOSE DROPS	TOTAL ORAL DOSE OUNCES	PERCENTAGE IMPROVEMENT 1938
M. L.	0.006	50	0.001	10 t.i.d.	$\frac{7}{8}$	95
F. W.	0.20	60	0.28	16 b.i.d.	$\frac{3}{4}$	85
N. L.	0.065	75	0.04	10 t.i.d.	$\frac{3}{4}$	95
H. R.	0.14	70	0.18	10 t.i.d.	$\frac{3}{4}$	90
L. H.	0.15	75	0.16	15 t.i.d.	1	95
S. C.	0.28	80	0.03	10 t.i.d.	$\frac{3}{4}$	90
H. M.	0.20	85	0.16	6 t.i.d.	$\frac{1}{2}$	95
P. M.	0.125	85	0.085	15 t.i.d.	1	95
N.E.	0.12	80	0.14	10 t.i.d.	1	90
S. G.	0.01	90	0.04	10 t.i.d.	1	100
W. K.	0.06	90	0.04	8 t.i.d.	1	75
A. S.	0.28	50	0.15	10 b.i.d.	$\frac{1}{4}$	25
H. J.	0.16	90	0.07	15 b.i.d.	1	70
P. F.	0.09	95	0.16	15 b.i.d.	$\frac{1}{2}$	75
S. V.	0.06	90	0.05	12 t.i.d.	1	70
L. T.	0.23	90	0.11	20 b.i.d.	1	75
J. V.	0.05	90	0.12	10 t.i.d.	$\frac{3}{4}$	80
P. G.	0.08	90	0.14	15 t.i.d.	1	80
V. P.	0.04	90	0.03	10 t.i.d.	$\frac{3}{4}$	90
J. L.	0.13	85	0.13	10 t.i.d.	1	85
J. H.	0.12	75	0.18	10 t.i.d.	$\frac{3}{4}$	75
S. L.	0.12	50	0.20	10 t.i.d.	1	50
S. H.	0.06	90	0.15	10 t.i.d.	1	90

EXPERIMENTAL

Several experiments were made to determine whether absorption of ragweed pollen extract through the bowel could be demonstrated. If we are to derive benefit from oral therapy, this should be demonstrated, unless a method other than that of our present conception is operative.

1. Five nonallergic individuals were injected intradermally with 0.1 c.c. of serum from an untreated hay fever individual whose serum had a high titer of reagins to ragweed. Each individual was then injected with

progressively increasing quantities of ragweed extract in the opposite arm. The first positive reaction (itching, wheal, and flare) at the passively transferred site was detected at a level of 0.2 c.c. of 0.1 mg. nitrogen extract, i.e., 0.02 total nitrogen. This was noted in 3 of the 5 subjects and occurred within two hours. The other two reacted at a level of 0.04 mg. total nitrogen. Cohen and his co-workers[5] had noted positive reactions in all subjects so tested with injections of 0.1 c.c. of 5 per cent ragweed extract. These subjects were now prepared with fresh serum of the same sample as in the previous experiment. They were then given 1 ounce of a 5 per cent mixed ragweed extract orally. The prepared sites did not react. Four were given 2 gm. and one, 5 gm. of mixed ragweed pollen by mouth the next day. Again, no prepared site reacted. This is in agreement with Bernstein and Kirsner[6] who used 5 grain quantities of ragweed pollen in the same way.

2. Blood serum was drawn from one individual who had taken 2 gm. of mixed ragweed pollen and from one who had taken 5 gm., twenty-four hours previously. The sera from these individuals were injected intradermally into 23 ragweed hay fever patients to note whether the ragweed active principle was present. Normal serum and buffered saline solution were used as controls. Intradermal tests were also made, using 0.02 c.c. of 0.001 mg. nitrogen and 0.0001 mg. nitrogen concentrations of ragweed extract, for purposes of comparison. Contrary to the experience of Black,[1] we are unable to report positive reactions of any consequence. Many showed questionable to one-plus reactions, but in each case the reactions were paralleled by normal serum. On the other hand, as one would expect, the ragweed extract tests showed from one- to four-plus reactions.

3. The above sera were now tested for ragweed active principle by injection into sites passively sensitized with serum containing reagins to ragweed. Again, contrary to the experience of Black,[1] no reaction took place even though the passively sensitized sites later reacted to 0.0001 mg. nitrogen ragweed extract.

DISCUSSION

Interpreting the significance of results obtained in the clinical work, due consideration must be given to the difficulties involved in obtaining an accurate determination of percentage of improvement, not only for the present year, but also for the year preceding. The psychologic influence of a new procedure must not be overlooked. Only if the differences were regular and quite marked could the estimates give a confirmed impression of advantage or disadvantage between the two methods. Besides this, certain variables must be taken into consideration: (a) the natural variability from year to year of a patient's tolerance independent of therapy; (b) the annual variations in pollen counts and annual differences in atmospheric conditions; (c) influence of previous

TABLE II

PATIENTS TREATED IN 1938 WITH COMBINED THERAPY, NOT TREATED IN 1937

PATIENT	MAX. DOSE MG. N	DAILY ORAL DOSE DROPS	TOTAL ORAL DOSE OUNCES	PERCENTAGE IMPROVEMENT
A. C.	0.04	8 t.i.d.	1	98
V. R.	0.01	15 t.i.d.	¾	95
J. H.	0.04	25 q.d.	1	95
B. S.	0.04	10 t.i.d.	1	95
E. P.	0.0006	10 t.i.d.	¾	90
J. B.	0.10	8 t.i.d.	¾	90
G. M.	0.006	10 t.i.d.	¾	85
E. E.	0.13	12 b.i.d.	1	85
A. B.	0.003	10 t.i.d.	½	75
T. G.	0.05	10 t.i.d.	¾	75
M. D.	0.07	10 t.i.d.	1	60
J. S.	0.4	10 t.i.d.	¾	50
B. W.	0.05	10 t.i.d.	1	50
G. K.	0.008	2 t.i.d.	½	50
M. C.	0.10	10 t.i.d.	1	50
L. L.	0.015	10 t.i.d.	¾	0
A. K.	0.11	20 b.i.d.	1	0

TABLE III

RESULTS OF TREATMENT WITH SUBCUTANEOUS THERAPY IN 1937

AMOUNT OF IMPROVEMENT		NO. PATIENTS	PERCENTAGE
Excellent	(85-100%)	13	56
Good	(70- 85%)	6	26
Fair	(50- 70%)	4	17
Poor	(Below 50%)	0	0

year's treatment has been shown by Vander Veer[7] to affect results in the subsequent year favorably; (d) differences in subcutaneous dosage for the two years under comparison. It is true, in our study, many patients who reported an improved year with combined treatment had a smaller subcutaneous dose than in the preceding year. On the other hand, some with a larger dose did not fare as well. Analysis of Table I shows that 10, or 43 per cent, of the patients fared better on combined treatment than on subcutaneous treatment alone. The improvement ranged from 10 to 45 per cent, the majority showing 10 to 20 per cent. On the same basis, 8, or 35 per cent, did not do as well by about the same margin. Five claimed no difference.

From Tables III and IV it is apparent that results in those patients on combined treatment in 1938 do not differ regularly nor significantly from results of patients on subcutaneous therapy alone in 1937. Table V indicates that results for all treated with combined therapy are not better than the results we are accustomed to expect from subcutaneous therapy alone. Considering the personal equation and variable factors involved, it would appear that, on the whole, combined therapy has added little to the orthodox subcutaneous therapy as far as improvement is concerned.

TABLE IV

RESULTS OF TREATMENT WITH COMBINED THERAPY IN 1938

AMOUNT OF IMPROVEMENT		NO. PATIENTS	PERCENTAGE
Excellent	(85-100%)	13	56
Good	(70- 85%)	8	34
Fair	(50- 70%)	1	4
Poor	(Below 50%)	1	4

TABLE V

RESULTS OF TREATMENT WITH COMBINED THERAPY FOR ALL PATIENTS IN 1938

AMOUNT OF IMPROVEMENT		NO. PATIENTS	PERCENTAGE
Excellent	(85-100%)	19	44
Good	(70- 85%)	12	29
Fair	(50- 70%)	8	19
Poor	(Below 50%)	3	7

The experimental work has shown that absorption from the intestinal tract, if at all, must be exceedingly small. It has been shown that a concentration in the blood, reached by the subcutaneous injection of as low as 0.02 nitrogen ragweed extract, will cause a reaction in an artificially sensitized site within two hours. Yet ingestion of 1 ounce of a 5 per cent mixed ragweed extract in 5 cases, of 2 gm. of pollen in 4 cases, and 5 gm. of pollen in one case, failed to reach this concentration. It was also shown that absorption, if any, from ingestion of 2 and 5 gm., respectively, in 2 individuals did not, after twenty-four hours, reach a concentration equal to 0.0001 nitrogen ragweed extract when tested on 23 ragweed patients. Again, a passively sensitized site which reacted to 0.0001 nitrogen ragweed failed to react to serum from individuals taken twenty-four hours after ingestion of 2 and 5 gm. of ragweed pollen. Furthermore, ingestion of 5 gm. of ragweed pollen failed to diminish the reactibility of a passively sensitized site twenty-four hours after ingestion. Further proof of infinitesimal absorption may be seen from our experience with a patient who had a constitutional reaction on a first injection at a New York hospital clinic. This patient's symptoms in past years were particularly severe. Despite extreme caution in our treatment, he had a constitutional reaction with 0.0002 nitrogen concentration of ragweed extract. This patient was able to take 25 drops of a 5 per cent ragweed extract orally with impunity. Still further proof that no appreciable amount of active principle enters the blood stream on oral administration is seen from the fact that constitutional reactions were no greater on combined therapy than with subcutaneous therapy alone.

CONCLUSIONS

1. Comparatively large doses of ragweed pollen extract may be taken orally, together with regular subcutaneous injections of ragweed extract.

2. Absorption of ragweed active principle into the blood stream from oral ingestion of ragweed pollen extract, if at all, is negligible.

3. Patients adequately treated by the subcutaneous method can expect no further benefit from oral ingestion of pollen.

REFERENCES

1. Black, J. H.: Oral Administration of Pollen, J. Lab. & Clin. Med. **12**: 1156, 1927.
2. McGrew, G. D.: Time and Money Saved in the Treatment of Hay Fever, Mil. Surgeon **80**: 371, 1937.
3. Stier, R. F. E., and Hollister, G.: Desensitization by Oral Administration of Pollen Extract, Northwest Med. **36**: 166, 1937.
4. Rockwell, G.: Oral Administration of Pollen and Treatment of Hay Fever, Ohio State M. J. **34**: 784, 1938.
5. Cohen, M. B., Ecker, E. E., and Rudolph, J. A.: The Effect of Allergy on Allergen Absorption Following Parenteral Injections, J. ALLERGY **2**: 453, 1931.
6. Bernstein, C. E., Jr., and Kirsner, J. B.: Oral Pollen Therapy, J. ALLERGY **8**: 221, 1937.
7. Vander Veer, A., and Clark, J. A., Jr.: Permanent Results Following Treatment for Late Hay Fever, J. ALLERGY **6**: 551, 1935.

UNUSUAL REACTIONS TO SLOW EPINEPHRINE*

JACK COHN, M.D.
SAN FRANCISCO, CALIF.

SINCE Keeney[1] first reported the symptomatic treatment of chronic intractable asthma with slow epinephrine in 1938, it has been used in the treatment of asthma and other allergic conditions with increasing frequency by the general practitioner as well as by the allergist. It is commercially available in 1 c.c. ampoules containing 2.0 mg. of epinephrine crystals in sterile peanut oil. This is the material upon which this paper is based.

It has been my experience that at times the use of this oily suspension of epinephrine is not without unpleasant, if not potentially serious, complications. It is true that in the great majority of patients who have been under my care, slow epinephrine has been administered without any unfavorable side reactions. As has been pointed out by Murphy and Jones,[2] the frequency of the injections of slow epinephrine is much less than that of adrenalin in a saline solution, and this is quite a factor in its favor. However, during the last three months I have had four experiences which, I believe, will bear investigation in their relationship to this new preparation.

In 3 of the 4 cases reported here, the patients were seen for the first time during severe asthmatic attacks. No record or history other than the patients' own statements as to their previous allergic studies was available. All stated that they had at previous times had similar asthmatic attacks and that these were relieved by injections of adrenalin which had caused the usual symptoms of slight nervousness, tachycardia, and excitement. In each of these cases the routine of epinephrine administration was as follows: 0.25 c.c. of a 1:1000 saline solution was injected subcutaneously. One-half hour later 1 c.c. of 2.0 mg. of epinephrine crystals in peanut oil was injected intramuscularly into the deltoid muscle, care being taken to draw back on the plunger of the syringe to be sure that the material was being emptied into the muscle itself.

CASE REPORTS

CASE 1.—J. L., a white female, aged 47 years, has had asthma for the last sixteen years. She stated that she had been studied and tested numerous times and had never given a positive reaction to any of the tests by either the scratch or intradermal method. Her severe attacks occurred every six to eight weeks and were

*From the Allergy Department, Mount Zion Hospital, San Francisco.

relieved by small amounts of adrenalin subcutaneously. She had an adrenalin spray, with 1:100 adrenalin, which she used almost daily to rid herself of mild symptoms.

The patient presented a typical asthmatic picture and was promptly relieved by the injection of 0.25 c.c. of a 1:1,000 saline solution of adrenalin. She complained of a slight nervousness following this injection that disappeared in ten to fifteen minutes. One-half hour after the first injection, 1 c.c. of slow epinephrine was given intramuscularly in the deltoid muscle, and the patient told to remain in bed. Approximately fifteen minutes after this last injection, she complained of feeling cold and dizzy, she started having a chill and perspired profusely. She became nauseated and vomited. Her lips were of a bluish tinge and there was a marked facial pallor. Her pulse rate was very rapid and of a weak quality. The foot of the bed was elevated and blankets and heat were placed about her. This reaction lasted ten minutes, after which she was perfectly normal, her asthma being greatly relieved. She complained of itching around the site of injection, and on inspection there was found to be a raised red area about 4 cm. in diameter. The next morning she complained of an eruption of a vesicular urticarial type around the site of the injection. This rash spread over the entire arm, neck, shoulder, back, and left breast, and lasted for two days. Calamine lotion with 1 per cent phenol relieved the itching.

CASE 2.—C. B., a white male, 64 years of age, was first seen while in status asthmaticus, unrelieved by 1:1,000 adrenalin solution in doses up to 2 c.c., repeated at hourly intervals three times. He was hospitalized, and aminophyllin was administered intravenously without effect. One cubic centimeter of epinephrine in peanut oil was given intramuscularly in the deltoid muscle. He suddenly became cyanotic, developed extreme dyspnea and vomited profusely. His pulse rate became thready. Caffeine, 0.5 gm., was given subcutaneously, and the patient was placed in an oxygen tent. The cyanosis and vomiting stopped after a few minutes, and the general condition of the patient became much the same as before the slow epinephrine was administered.

CASE 3.—W. L., a white boy 12 years of age, was seen during a mild asthmatic attack. One-fourth cubic centimeter of adrenalin (saline solution 1:1,000) was given subcutaneously, with marked relief after ten minutes. The breathing became easier and the youth appeared to be relieved. One cubic centimeter of epinephrine in oil was given intramuscularly in the deltoid region, and within five minutes the boy became very pale, complained of headache and nausea, and appeared very apprehensive. These symptoms gave way to prolonged vomiting. He complained of itching at the site of injection, but nothing could be seen. This stopped after about an hour.

CASE 4.—C. A., a white male, aged 24, was seen with giant urticaria, especially of the lips and tongue. His skin tests showed a multiple sensitivity to foods, among which was a reaction to peanuts. He also reacted to many epidermals and pollens. During the attack herein described, he complained of a swelling of his tongue and lips. The latter were so engorged that the skin was cracked in several places, exuding serum. He complained of severe itching around the border of the swelling. Adrenalin (0.25 c.c.) was given subcutaneously with slight abatement of the itching and after thirty minutes, 1 c.c. of epinephrine in oil was given intramuscularly in the deltoid region. About five minutes after administration of the slow epinephrine, a redness appeared at the site of the injection and spread gradually in the course of four hours over the entire forearm. It became swollen and red and itched intensely. Relief was obtained by using cold magnesium sulfate compresses. This reaction lasted for about eighteen hours, and the involved area remained refractory for ten days to intradermal tests of substances to which the patient had previously given positive reactions. The other arm was used and typical allergic responses were elicited.

COMMENT

As is obvious, this report is inconclusive because of the small number of cases reported and also because of the lack of an experimental control group. However, it can be seen that the use of epinephrine in peanut oil is not without its dangers and should not be given promiscuously. Peanut oil as a vehicle for epinephrine, after all, is perhaps not an ideal one and should be used cautiously because of a possible underlying hypersensitiveness to peanut as well as side effects, the nature of which is not as yet understood.

Slow epinephrine is of value in many cases of allergy, as shown by Keeney,[1] and Murphy and Jones.[2] Its advantages are that it distinctly decreases the number of injections necessary for the control of the allergic condition, and it is not used up as quickly as epinephrine in other forms. Its disadvantages are that untoward side reactions may occur that are distinctly discomforting to both the patient and the doctor.

SUMMARY

Four cases are reported in which slow epinephrine was used with the following unusual symptoms: nausea, vomiting, chills, vesicular urticaria, cyanosis, increased dyspnea, and swelling and edema of the forearm.

REFERENCES

1. Keeney, E. L.: Slowly Absorbed Epinephrine Preparation. Preliminary Report, Bull. Johns Hopkins Hosp. **62**: 227, 1938.
2. Murphy, J. A., and Jones, C. A.: Slow Epinephrine in the Treatment of Chronic Asthma, J. ALLERGY **10**: 215, 1939.

450 SUTTER STREET

THE PRACTICAL APPLICATION OF THE ALLERGY-TESTING TABLE*

J. Warrick Thomas, M.D.
Cleveland, Ohio

THE purpose of the allergy-testing table is to enable the allergist to make certain studies on his patient and, at the same time, to conserve his time by having the patient comfortable and more accessible. This table is a modification of the one illustrated in Vaughan's *Practice of Allergy*.[1]

Fig. 1.

Some of the advantages of the allergy-testing table are:

(1) The patient is more accessible and more tests may be applied in a shorter interval of time if the technician is standing rather than sitting.

*From the Cleveland Clinic.

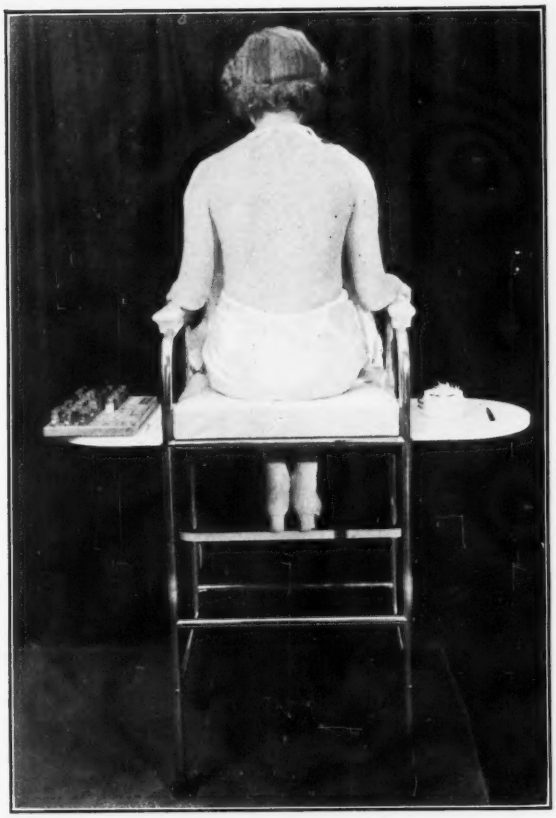


Fig. 2.

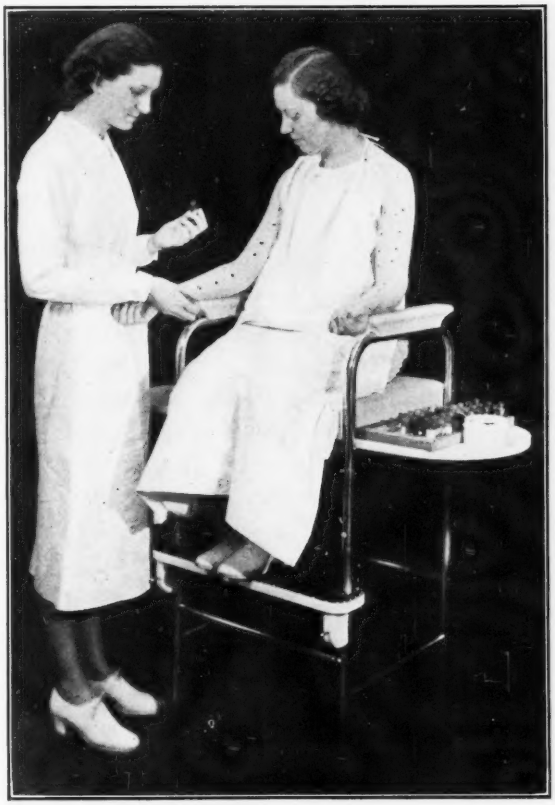


Fig. 3.

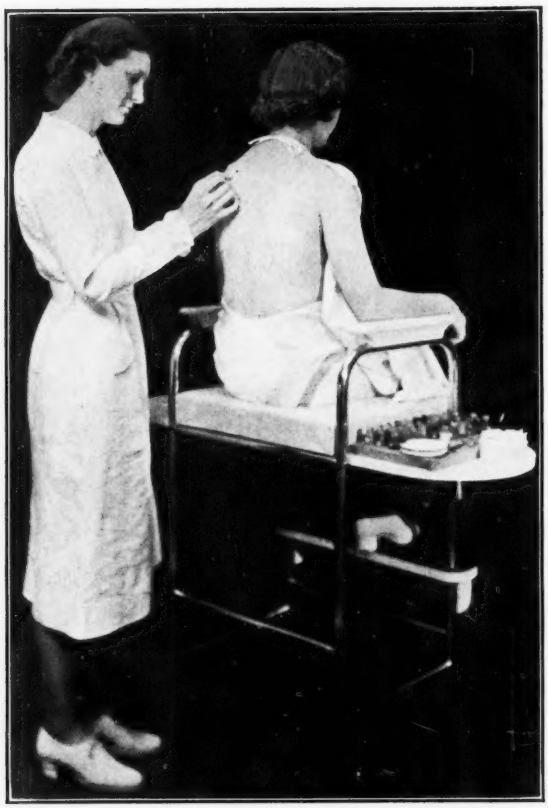


Fig. 4.

(2) The patient is comfortable; he has a spring cushion, arm rest, and foot rest, which is adjustable to the various leg lengths.

(3) A child may be supported by an assistant standing in front of the table while the tests are applied to his back, with a minimum movement of the child.

(4) The arms of the patient are supported while the tests are applied and during the interval required for full reading of the test.

(5) The time required for application of a group of tests is shortened.

(6) The table is used not only for routine skin testing but also for patch testing, ophthalmic tests, nasal contact tests, and certain tests for physical allergy. It may be used in chest and other examinations.

(7) The chair enables one to have the testing material in close proximity with the patient.

(8) Space for the patient, testing table, materials, and apparatus are minimized. This piece of equipment may be transferred from one locality to another, depending upon circumstances.

(9) Rubber tips on the table legs and a rubber mat on the adjustable foot rest or step prevents the table from skidding or the patient from slipping while being seated.

REFERENCE

1. Vaughan, W. T.: Practice of Allergy, St. Louis, 1939, The C. V. Mosby Co.

Society Proceedings

SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

ANNUAL MEETING, ATLANTIC CITY, N. J., APRIL 29, 1939

Antigenic Studies by the Dale Test. STANLEY F. HAMPTON, M.D., ARTHUR STULL, PH.D., AND ROBERT A. COOKE, M.D., New York, N. Y. (Abstract.)

The antigenic relationship of low and giant ragweed pollen, timothy, and orchard and June grass pollen was studied in experimentally sensitized guinea pigs, using the Dale test.

Guinea pigs were sensitized by intraperitoneal injection of the alum-precipitated pollen extract, and after a lapse of at least three weeks, the Dale tests were performed.

Each uterine horn was tested with a related antigen, a ragweed or a grass pollen extract other than the one used in sensitization, as well as with the specific pollen antigen used in sensitizing.

In 36 experiments, a related antigen always produced a positive Dale reaction. Although the specific antigen always neutralized the uterine antibodies against the related antigen, the related antigen did not always neutralize against the specific antigen. This was true in both the ragweed and the grass pollen groups. These results signify a close antigenic relationship, but not a true identity of the ragweed pollens and of the three grass pollens studied.

Using the same technique, alum-precipitated stock house dust extract sensitized 12 of 14 guinea pigs. Three animal epithelium extracts, namely, dog epithelium, cat epithelium, and combined feathers, produced contractions, but did not neutralize the uterine antibodies to the specific house dust extract (extract used in sensitization). This signifies the presence of some antigenic factor in house dust extract other than common inhalants tested.

Serological Changes Resulting From the Treatment of Hay Fever Over a Period of Years. WILLIAM B. SHERMAN, M.D., AND ARTHUR STULL, PH.D., New York, N. Y. (Abstract.)

Sera of 55 patients with hay fever treated for two to twenty-three years were studied by dilution and neutralization tests. During the first few months of treatment there was usually an increase in the amount of skin-sensitizing antibody. After two to five years of treatment, there was

a progressive decrease of antibody until many of the patients treated ten or more years did not transfer sensitivity. The amount of pollen extract required to neutralize the sera was increased during the first two to five years of treatment, but subsequently showed a decrease. The changes in dilution and neutralization were not always parallel, suggesting a qualitative change in the antibody. The sera which no longer sensitized skin showed little or no evidence of blocking antibody.

Sensitizations Induced by Tetanus Toxoid. Robert A. Cooke, M.D., Stanley F. Hampton, M.D., William B. Sherman, M.D., and Arthur Stull, Ph.D., New York, N. Y. (Abstract.)

This study of induced allergy was stimulated by the observation of a constitutional reaction in a patient immediately following the second injection of tetanus toxoid. Chemical and immunologic studies show that this was due to the proteose fraction in the toxoid. The importance of this and various implications arising are discussed, as well as the importance of methods of prevention.

SYMPOSIUM ON THE PRACTICE OF ALLERGY*

RICHARD A. KERN, M.D., PRESIDING

DR. KERN.—The presentations which follow I am sure will be of great interest and importance to all of us, for they deal with practical matters with which we are confronted every day of our lives. The first four speakers will consider various phases of *Clinic Activities* and *Clinic Facilities.*

The clinic is probably the most important means of supplying the community with those qualified to practice allergy. Therefore, the mode of conducting clinics demands careful consideration so that properly trained allergists be turned out. A clinic should not be simply a shop to grind out cases: there should be a limitation of the number of patients seen and staff members should be encouraged and guided in research.

The symposium opens with remarks on

The Role of the Clinic in the Training of Allergists. FRANCIS M. RACKEMANN, M.D., Boston, Mass.

It has been said that "Education consists in the training of the individual to teach himself." This statement applies directly to allergy. It is difficult, probably impossible, to teach the subject of allergy so that the student will have seen every possible type of case and will understand every detail of mechanism, diagnosis, and treatment; but it is not difficult to give the student the new point of view which the study of allergy provides. It is not difficult to show the underlying fundamental principles. This demonstration can be given by lectures with fair success, but the clinic and the living patients in it make a demonstration which is more satisfactory.

The objects of the clinic are three: to take care of the patient; to study his case in relation to the other cases; and to use his case in teaching. Students are always welcome because their mere presence encourages greater care in diagnosis and treatment. They are of three types:

1. *Undergraduates* want to know what allergy is all about, and they can be shown in a relatively short time, just as a rough impression of a new city or even of a museum can be obtained in a brief visit. To find that there is a considerable number of patients whose symptoms depend, not upon something obviously wrong with their anatomy, but upon some change in the environment or in the diet, and that these symptoms can be removed by the elimination of one or other extrinsic factor, provides in itself a new point of view. To listen to

*The second of two symposia presented at the Fall Meeting of the Society for the Study of Asthma and Allied Conditions, New York, N. Y., December 3, 1938.

a demonstration of the tricks in taking the history of an actual case is instructive, and then to watch the technique of making, observing, and recording skin tests, is dramatic, particularly when it becomes possible to bring the history and the tests together to make a diagnosis which is both sensible and rational. One or two visits to the clinic may be all that is necessary for the intelligent student to get an idea of what allergy is all about.

2. *Practitioners* want to know more, and they must stay long enough to learn the point of view and become quite familiar with certain general principles. The older student must know that allergy depends chiefly upon a changed reaction in the host. The tendency or capacity to become sensitive is inherited; the particular sensitiveness is acquired by individuals who have that tendency. He must know that the nature of the tendency is quite unknown. Asthma depends upon allergy; at least in many cases, the attack is initiated by an exposure to some foreign substance. In other cases, however, the relationship between the attack and the exposure is not so close. There is reason to think that not all asthma is allergic. The older person presents the typical picture of chronic pulmonary emphysema—of "idiopathic" origin. Another has "cardiac" asthma, and a third, pulmonary fibrosis, or even silicosis. Lesions of the sinuses are so common as to be part of the whole picture. Eosinophilia is another part. These other patients wheeze; they too have "asthma," and this kind of asthma must be correlated with the more typical extrinsic variety. The term "intrinsic" asthma has a real application and may be found to rest upon a substantial basis dependent on a fundamental physiologic change. Meantime, injections of histamine, of acetylcholine, or of peptone have been found to reproduce the symptoms of asthma.

These isolated bits of clinical information are being assembled slowly. Mention of them should be included among the "general principles" which the practitioner should learn in addition to the little that we can teach him about methods of treatment which are really effective. How long this instruction will take, will depend upon the individual. With his limited time, the graduate practitioner need not—indeed he cannot—attempt to learn every detail. If only he can be persuaded to keep his mind open—wide open—he will have learned a lot.

3. *There are men who really want to work in allergy* and obtain a thorough knowledge of the subject. These men can be taught best by setting them to work on one or more definite problems to which they can apply their full time and attention for a year, or, better, for two years. At the end of that period, they acquire a broad understanding of allergy; they become familiar with the literature; they learn to study and treat patients of many kinds; they attend meetings to learn the faces as well as the names of the authors of many papers; and finally, they complete and publish the results of their own work; and so take their place in the front rank. Incidentally, and during their term of service, they are thrown with other young men working intensively on other subjects, and so they learn something about medicine in general. The critical attitude which comes as a by-product of their training is probably the best part of it. They become experts in allergy; they are qualified to continue their own researches; and they are qualified to teach. They are a credit to themselves and to the clinic from whence they came.

In the presence of inquisitive students and of research workers, the work done in the clinic must be good. If the clinic is to teach properly, its work must be of high standard to serve as a model for its students to follow.

DR. KERN.—Inquiries are constantly coming to the Joint Committee on Standards as to what a satisfactory Allergy Clinic needs in the way of proper facilities, medical and technical staff, and equipment. The next three speakers will deal with various angles of this subject. There comes now a discussion of

Personnel and Equipment. WILL C. SPAIN, M.D., New York, N. Y.

The staff of the allergy clinic might well be divided into two groups, the medical and the nonmedical. The first group is composed chiefly of physicians trained in internal medicine, but as you have heard so frequently, the boundaries of allergy are so extended, that it is impossible for the subject to be adequately handled by the internist alone, no matter how well versed in this specialty he may happen to be. It is for this reason that the well-appointed allergy staff should have among its members a pediatrician and a dermatologist as consultants.

If the admissions warrant, the allergic children may be segregated into a separate clinic, its pediatric division manned by physicians trained in childhood diseases. Similarly, the dermatologic cases may be handled. In any event, whether the pediatric or dermatologic cases be treated in the general allergy clinic or in special divisions, there must be available a consulting laryngologist, to whom problems in allergy may be taken for an investigation of possible upper respiratory foci. There should be a complete nose and throat room at the disposal of the allergy clinic in direct physical connection with the clinic, so that the member of the staff may take his patient and findings directly to the rhinologist for consultation, and not be forced to travel down corridors or up flights of stairs to some remote spot. Where possible, the medical staff should also have a research fellow in allergy, or a resident student, devoting himself to research problems and taking advantage of the clinical material in the various branches of this specialty.

In the nonmedical group of the staff, the social service worker is important. This person should really be designated as an investigative worker, since it is her responsibility, not only to inquire into the financial status of the patients applying for treatment, but also to follow up in the home the recommendations of the medical portion of the allergy staff. It is highly important for her to inquire as to whether the proper changes have been made in the home environment, and if the diets have been followed, based upon the diagnosis of the clinic. It is of very little value to find that an asthmatic patient reacts to rabbit epithelium, and that he has been sleeping upon a rabbit hair pillow, unless he can be convinced that this article of bedding is dangerous for him, and that he understands that its complete removal from the home is necessary. Only the trained investigative worker can take care of such problems.

In addition to the nurses in this nonmedical group of the staff, whose duties are obvious, there should be a technician in charge of the preparation of vaccines and extracts for use in the clinics. Such

a technician should be trained primarily in bacteriologic methods. Where possible, a research worker, unhindered by routine, should be engaged in problems of general interest in the clinic.

It goes without saying that there should be easy access to the wards for the placement and study of clinic patients requiring hospitalization.

The equipment of the allergy clinic may be divided into two portions, the first of which may be termed the physical, and the second of which I would like, at the risk of being suspected of evangelism, to call the spiritual. Under the physical would come the necessary icebox storage facilities in both the clinic and the laboratory, nose and throat diagnostic utensils; in the laboratory, apparatus for estimating nitrogen content of extracts, bacteriologic equipment for the preparation of vaccines, and the checking of sterility of extracts. The spiritual equipment, to be encouraged in every member of the staff of the medical and nonmedical groups, should be derived from frequent discussions and conferences. Regular clinical conferences of the whole staff should be held also, where routine matters may be discussed, plans may be laid, research problems considered, and recent literature surveyed.

DR. KERN.—The next speaker has some very useful and pertinent things to say on

The Preparation of Extracts. MILTON B. COHEN, M.D., Cleveland, Ohio.

Every laboratory test has a degree of sensitivity and a degree of reliability. The most refined serologic tests for syphilis, for example, give positive reactions in more than 95 per cent of cases of proved syphilis and only 2 to 3 per cent in cases where the positive reaction cannot be correlated with the clinical diagnosis. The skin test is a laboratory procedure and must be evaluated with respect to its sensitivity and reliability. Experience has demonstrated that properly performed skin tests have a high degree of sensitivity in detecting inhalant allergy and that the tests disclose the etiologic agent in over 90 per cent of cases, having, therefore, a high index of sensitivity and of reliability. Skin tests with food extracts, however, give positive reactions in a much smaller percentage of clinical cases of food sensitivity and fewer of the positive reactions can be shown to be of etiologic significance. It is fair to state that not more than 50 per cent of the significant foods can be detected by immunologic methods.

The exact nature of the substances giving skin reactions (allergens) is not known. They are, however, all water soluble, and because of the speed of reaction after contact with sensitive cells, probably readily diffusible and of relatively small molecular size. Chemical treatment of extracts is as likely to diminish their activity as to enhance it. The substances which elicit the clinical reactions contact the body in their crude form. It is logical, therefore, to prepare extracts with the minimum of chemical treatment consistent with obtaining preparations which react in known sensitive individuals and give few false reactions.

For the past ten years we have prepared crude extracts as follows:

1. All fruits and vegetables which are juicy are ground in a meat grinder. The juice is pressed out and is filtered under toluol into a

sterile bottle through ordinary filter paper. To the clear juice, an equal amount of glycerin is added. Fruits which jell must stand under toluol until the clot shrinks. The clear fruit serum is used instead of original juice.

2. All dry foods, animal danders, orris, and similar powdered substances.

Grind if necessary—defat. Place sufficient dry material in a pint jar and fill it about 2 inches from the bottom. To this add 0.85 per cent saline in sufficient quantity to wet the dry material thoroughly and to cover the moistened powder to a depth of 2 inches. Cover with toluol. Extract at room temperature overnight. Filter through ordinary filter paper and add an equal amount of glycerin.

3. House dust.

Place a double handful of the dust to be extracted in a cellophane dialyzing bag. Saturate thoroughly with water (Cleveland tap water is satisfactory, others may not be), and add a very slight excess of water. Cover with toluol. Dialyze in running water for forty-eight hours. Extraction and dialysis will be proceeding concomitantly. Remove from bag. Filter through paper and Seitz filter. Dissolve in the sterile extract sufficient sodium chloride to make 0.85 per cent, and add an equal amount of glycerin.

4. Pollens.

Weigh out pollen—defat. Place in solution consisting of equal parts of glycerin and 0.85 per cent salt solution. Cover with toluol. Extract twenty-four hours. Filter through paper and Seitz.

5. Egg.

Prepare by sterilizing egg white under toluol. Add equal amount of glycerin.

6. Milk.

Separate fat from skim milk using a tall burette. Neutralize with sodium bicarbonate. Seitz filter and add an equal amount of glycerin.

No attempt is made to do nitrogen estimations on these extracts. Scratch tests are performed with the glycerinated extracts. In this manner the best reactions will be segregated. Negative scratch reactions are repeated by the intradermal technique, using 1:50 dilutions of the glycerinated extracts in 0.40 per cent phenol in 0.85 per cent salt solution.

When using extracts prepared in this manner for treatment, one makes dilutions in 50 per cent glycerin, 50 per cent saline solution. Sufficient pollen should be purchased at one time so that the same material will be available for the preparation of batches of extract for several years. This insures a standard extract for use during that period. Similarly, we use old cotton linters of high dust content for our house dust extract, having on hand a supply good for several years.

For a long time we have objected to the injection of glycerinated extracts in treatment because of the pain produced, but have preferred them because of their relative stability. During the past year we have extracted pollens and house dust in aqueous solutions and have dried the extracts in a lyophile dryer. The dry material is taken up in the proper amount of 0.85 per cent saline when needed for use. In this way it is possible to prepare a year's supply of pollen extract and to preserve it without deterioration.

In outlining this simple method of preparation of extracts for use in allergy, I am not attempting to decry attempts to produce better extracts. Perhaps we may some day know the exact nature of each allergen and will be able to standardize our extracts with exactitude. Until that time, and for clinical purposes only, extracts prepared as here outlined will give satisfactory information when used with sound clinical judgment. Clinical experience will always be more important than skin testing in the management of individuals with allergic manifestations. Time spent on better clinical work will yield more than time spent on improvement of extracts because of the problems of sensitivity and reliability mentioned in the introduction.

DR. KERN.—Those who have served on the Joint Committee on Standards feel keenly the need for some sound advice to clinic directors on the matter of adequate records of patients in an allergy clinic. The next presentation is on

Clinic Records. NATHAN B. HERMAN, M.D., Baltimore, Md.

The primary purpose of clinical records is to facilitate the immediate study of cases of disease and to constitute adequate material for subsequent investigation of such cases. The less complicated the record, provided it is adequate for the above purposes, the more serviceable it will be. The actual form of the record will, of course, be determined by the practice of the individual institution, since uniformity is important. A unit history, in which are assembled all of the data pertaining to the patient, has proved to be most satisfactory, and such a unit should be filed in an accessible, central history room.

The history should include a conventional medical history plus a detailed account of the development of the suspected allergic complaint under investigation. The more specifically one can note the historical data covering the allergic disease, the more valuable the record will be. Especial attention should be paid to the actual time sequence of the appearance of symptoms. Unfortunately, in clinic experience, such detailed information is often well-nigh impossible to obtain, but this should not discourage the effort. Since successful treatment so often depends on diagnostic clues obtained from the history, the importance of painstaking gathering of significant details cannot be overstressed. Blank forms, to be checked in the affirmative or negative, are not satisfactory. In addition to the actual history, the record should contain a complete physical examination and a certain minimal amount of laboratory data. Just what this minimum should include is debatable, but a blood Wassermann or Kahn and a urinalysis are not too much to ask. Where indicated, blood studies, sputum examination and culture, and smears of nasal secretion should be obtained. X-ray investigations, of course, play a prominent role in the work-up of many cases. The services of special consultants, especially laryngologic and dermatologic, are frequently necessary, and their reports should be incorporated in the general record.

Having obtained such data, the study and analysis follow relatively easily. The progress of the patient is followed by short notes, and any pertinent details missed in the initial history, but gathered by subsequent observations, may be included. A front sheet diagnosis may now be added. This will necessitate a careful review of the

entire record. The importance of such a review is great. Omissions in the study can be then caught up and rectified. While it is impossible to foresee all the demands that subsequent research may make on an individual case, certain standard requirements should always be met. If these requirements are lacking, the necessary corrections and additions can be made while the case is fresh and the patient still in attendance. With the addition of a final diagnosis and the placing in the disease index file, the record should then be available for future investigation.

A number of nonmedical services frequently contribute to a complete case study. The report and appraisal of a trained social worker are often essential to the proper appreciation of a clinical situation. The social service summary and recommendations should be included in the clinical record. The same applies to the participation of the dietetic department. Special reports, such as diary cards of hay fever cases, should form a part of the record, so as to be readily available for yearly comparison. If one were to sum up in a few words the criteria of good clinic records, one could give *completeness, accessibility,* and *simplicity.*

DR. KERN.—The closing topic of this symposium is one that directly concerns each and every one of us: the problems that arise in the private practice of our specialty. Just what is the province of the practitioner of allergy? Should he really be a doctor, or just a glorified technician? What of his relations to referring physicians? The speaker to whom the subject has been assigned has amply proved himself to be especially well qualified to present it. In a busy private practice our president has exemplified the highest ideals of scientific study and research as well as of ethical procedure. The symposium ends with the discussion of

Allergy in Private Practice. WARREN T. VAUGHAN, M.D., Richmond, Va.

The first point that I would emphasize is that allergy is a subdivision of internal medicine and cannot be divorced from the latter. In the private practice of allergy, one has ample opportunity to apply this principle. The approach to each case should be that of the internist. This includes a physical examination, even in a case of simple hay fever, the various indicated special laboratory studies, etc. Such a procedure is relatively easy in private practice where there is no great rush and the patient is inclined to be disappointed unless a lot of work is being done in the investigation of his case.

This opportunity for detailed study facilitates exploration in the borderlands of allergy. It is the internist investigating allergy rather than the asthma and hay fever specialist who may be expected to add hitherto unsuspected diseases to the list of those in which allergy may play a part, such as purpura, thromboangiitis obliterans, mucous colitis, migraine, peptic ulcer, periarteritis nodosa, and the like. A prominent allergist recently made the statement that he had never seen cases of allergic migraine. His work is in a large clinic in which the patients are assigned to men in special fields of interest. The only explanation that to me seems tenable is that the cases of allergic head-

ache or migraine are assigned to different departments. The same applies to some who are interested primarily in respiratory allergy, and are inclined to underestimate the importance of food allergy.

The man doing clinic work, as well as private practice, is sometimes inclined to limit his investigative work to the clinic cases. Although his approach to an allergic problem may be that of internal medicine in his office, that in his clinic is often limited to one particular phase of allergy, such as asthma and hay fever or dermatitis. In the clinic there is often a subconscious reaction to the borderland or borderline case, with a tendency to pass it on to another division of the clinic, labeled "not clearly allergic." The press of material awaiting treatment contributes to this.

This is to be contrasted with office procedure. Take the matter of nasopharyngeal catarrh as an example. Much so-called sinus disease is actually allergic rhinitis. Many a patient who has been treated locally for sinus disease for years, eventually finds his way to the allergist's office, where he receives the first real relief. Going home, possibly to a distant town, he tells his friend, also suffering from "sinus disease" and also unrelieved, whereupon the friend, either with or without the consent of his physician, makes the long journey to the distant allergist. The allergist discovers very little evidence of allergy, and that the patient actually does have some sinus infection with a postnasal catarrh. The patient in common with nearly everybody else may give a history of some minor allergic manifestation at some time in the past and not infrequently gives positive skin reactions to at least a few allergenic substances.

Now this man has traveled 200 miles for an allergic diagnostic study. He has previously convinced himself that he should have this study. Should he be sent back home with the assurance that allergy is playing no part whatsoever and without diagnostic study? Can you be sure that allergy is not playing a part?

In our own work we have felt that we cannot be sure and we have not had the heart to send the patient home, utterly disappointed. We have explained to him frankly that the chances are against allergy being of importance, but that we will proceed with the studies in the hope that it may develop that allergy is at least playing a part of secondary significance and that, this being controlled, the treatment of the actual sinus infection may be more successful.

In a surprising number we have found that this combined method of allergic and local rhinologic therapy, in persons in whom the allergic factor appears at first blush to be of very little importance, has given more relief than any other measure or combination of measures previously attempted. We have found this so often as to justify allergic study in this type of case. In the same way we have found that a number of cases which appeared to be simple bronchitis have an allergic background. Control of the latter facilitates treatment of the former. In clinic routine these cases would have been shunted to the other departments and would have lost the opportunity for allergic investigation.

The approach through internal medicine to the study of an allergic case in private practice has an educational value, in showing the patient that skin testing is far from the entire story in an allergic investigation. The physician has time and the inclination to sit with the patient, discuss his problems and his past experiences in detail,

and to explain to him that his allergic reactions are but a part of the reaction of the body as a whole to its environment.

What of the discussion with he patient and with his doctor, at the termination of the allergic diagnostic study? When the patient comes in for diagnosis and subsequent treatment, and the allergist will continue in charge, there is no great problem. The real problem of gaining effective cooperation is with the patient who is referred by the family physician who will later undertake to carry out the therapeutic program as outlined for him by the allergist. In my own practice by far the majority of patients are referred from a distance. After the completion of the study, a detailed report must be made for the physician who will of necessity continue the treatment. The consultant has two responsibilities, to the patient and to the referring physician. The physician has sent the patient because he wanted help. He has tried all of the therapeutic measures available without success. It is up to the consultant to provide him with other more effective measures and tell him how to use them. In my experience the attending physician in this type of case welcomes continued interest and cooperation from the consultant. As a rule, he would rather have the consultant take over the entire vexing problem but on account of distance he realizes that this cannot be done and is perfectly willing to carry out orders.

The consultant's responsibility to the patient does not terminate with the completion of the examination. The patient may think that this will be all that is necessary for relief, but the allergist knows that in many cases weeks, months, or even years of close supervision are necessary before best results may be obtained. Since the patient may not know this, it is the duty of the consultant to provide him with this facility. Our discussion with the patient at the termination of the study is, therefore, somewhat as follows:

"Dr. Blank has sent you in because he wants us to help in the treatment of your case. Although you may be rapidly relieved after treatment is instituted, it may require weeks or months before relief is adequate. I shall, therefore, want you to write in to me at frequent intervals, say once each month, reporting to me how you are getting along, in what ways you are doing well or poorly, so that I may write Dr. Blank additional suggestions concerning treatment. Dr. Blank will also be writing when he needs more of your treatment extract, but I shall want you especially to write, because he is a very busy man and you will be able to give me details which he cannot.

"In this way I shall keep in quite close touch with you for at least a year, through the four seasons, since different factors play a part at different seasons of the year. After that I will also keep in touch with you, but there will probably not be need of as frequent reports."

In this way correspondence is continued with both the doctor and the patient. At the start the doctor receives copies of all the tests that have been performed, all the laboratory studies, a report of the physical examination, an outline of treatment, and special directions to cover avoidance or hyposensitization. With patients coming from a distance it is best to do at the beginning all of the tests that may be needed, since he cannot visit the office frequently. With an adequately complete original survey, it is surprising how much treatment may be administered in a proper manner with the aid of the local physician and through the medium of correspondence.

One phase of the subject of private practice invariably comes up for discussion. This is the matter of charges. Our principle has been briefly that while the charges for the original diagnostic study should be commensurate with the amount of work done, those for further care, in other words, for treatment, should be made as reasonable as is in any way possible. The doctor knows beforehand that treatment must be long continued for adequate relief. If by his charges for return visits he makes it impossible for the patient to continue with treatment, neither he nor his victim derives any benefit from the set-up. In our own work we keep subsequent charges at a surprisingly low level, charging by the month, quarter, or year rather than by the visit. Laughingly we have at times described the charges as initiation fee and dues. One more seriously inclined might describe them in legal phraseology as "retainer fee."

What are the facilities for clinical investigation—for research in private practice?

In allergy probably more than in any other phase of clinical medicine, the patient is almost invariably delighted to cooperate in experimental studies. He realizes that this is a new field of medicine, one in which investigation is proceeding at the present time, and he is subconsciously delighted to find that his doctor is contributing to knowledge in the field. The patient in private practice is usually a responsible member of society, not a bird of flight, and when after a year or two or more the physician wishes to make a follow-up study of the progress of his case, he can usually find his patient without difficulty, a feat which is often not accomplished in charity clinic work.

Even in the field of medical education as it applies to allergy we have found that private practice has some distinct advantages over clinic work, provided the amount of material is adequate. One does not need as much since each case is studied so much more comprehensively. For ten years we have conducted a training school for technicians, emphasizing allergy technology, and in the last three years we have had residencies for physicians desiring special study in the field. The training with both groups has been that of internal medicine as applied to allergy. It is quite possible that these students have achieved a broader perspective than they would have, had their studies been restricted to the norrower fields of clinic practice.

THE AMERICAN SOCIETY FOR THE STUDY OF ALLERGY

Resolution

WHEREAS, the Society has heard of the tragic death of Salvator Parlato, and

WHEREAS, the Society has suffered the loss of one of its most valuable, beloved, and honored members through this tragedy, and

WHEREAS, his amiability, industry, and character were an inspiration to all who knew him, and

WHEREAS, his contributions to the field of Allergy will remain long outstanding into the future, be it therefore

Resolved, That we, the American Society for the Study of Allergy, formally and sincerely record the realization of our misfortune and that of the profession in general to his untimely passing, and be it further

Resolved, That a copy of these resolutions be set upon the minutes of the Society, a copy be forwarded to his wife and family, and a notice be published in the official JOURNAL of the Society.

J. HARVEY BLACK, Secretary.

THE JEWISH HOSPITAL OF BROOKLYN

ALLERGY DIVISION, BROOKLYN, N. Y., MAY 22, 1939

Absorption of Undigested Protein From the Stomach, Esophagus and Gall Bladder in the Rhesus Monkey. MAX HARTEN, M.D., IRVING GRAY, M.D., SAUL LIVINGSTON, M.D., and MATTHEW WALZER, M.D. (Abstract.)

Cutaneous sites were sensitized in the monkey by the intracutaneous injection of human sera containing reagin antibodies for cottonseed in high titer. Forty-eight hours later, the animals, under nembutal anesthesia, were operated upon and tested. The test meal consisted of either cottonseed extract (0.57 mg. N per c.c.) or cottonseed "milk," made by dissolving 10 gm. of raw ground cottonseed in 30 c.c. of water.

To study absorption from the stomach, the stomach was sectioned at the pyloroduodenal junction and clamped. The test meal was then introduced into the stomach through a catheter in the esophagus. In another animal the stomach was clamped and sectioned at both the pyloroduodenal and the cardioesophageal junctions, and the antigen was injected, with a syringe, into the stomach through the wall. The sensitized cutaneous sites reacted in from eight to eighteen minutes after introduction of the cottonseed, demonstrating the absorption of antigen into the circulation from the stomach.

To study absorption from the isolated esophagus, the esophagus was clamped and cut at both ends. Seven cubic centimeters of cottonseed "milk" were then introduced into the esophagus through the upper opening. The cutaneous reaction developed in ten minutes.

In the gall bladder experiments, the first portion of the common duct in one animal and the cystic pedicle in another were clamped. In each instance bile was withdrawn from the gall bladder by syringe, and 1 c.c. of cottonseed "milk" was injected in its place. Positive cutaneous reactions developed in six minutes. In this manner the absorption of unaltered protein from the stomach, esophagus, and gall bladder in the *Rhesus* monkey was demonstrated.

The Pathology of the Allergic Reactions in the Passively Sensitized Tissues of the Macacus Rhesus Monkey. DAVID GRAYZEL, M.D., and MATTHEW WALZER, M.D. (Abstract.)

Sensitization of the skin and organs of the *Rhesus* monkey was accomplished by the injection of human reagin-bearing serum. The allergic reactions were induced forty-eight or seventy-two hours later by the

intravenous injections of the specifically related antigen. Specimens of the reacting tissues were fixed in 10 per cent formalin, Zenker's solution, and Bouin's solution, embedded in paraffin and stained with hematoxylin and eosin.

In the gall bladder the reaction manifested itself grossly by the loss of the surface granularity of the mucosa and by edema. Histologic examination showed that the lamina propria was broadened by edema, the blood vessels were engorged, and there was an infiltration of tissues by eosinophiles, small round cells, mononuclear cells, and some polymorphonuclear leucocytes. These changes also involved the intermuscular and perimuscular connective tissue. In the intestines the gross reaction manifested itself by blanching and thickening of the wall due to edema. Histologically there was edema, congestion of the vessels with some margination of white blood cells, and a cellular infiltration similar to that seen in the gall bladder. These changes particularly involved the submucosa and serosa. The sensitized mesentery showed changes similar to those noted in other tissues.

Sections of the allergic cutaneous reaction were taken at intervals of from five to fifteen minutes for a period of two hours. The inflammatory process was progressive. It began with edema and some vascular congestion. Later margination of white blood cells within the vessels was noted. This was followed by a cellular infiltration beginning at first in the vicinity of the vessels and then spreading through the entire tissue. Histamine wheals induced by intracutaneous injections of histamine solution 1:1000 were similarly studied for comparison with specific wheals. These reactions on the whole were similar to the specific ones but were less marked.

Studies in Guinea Pig Anaphylaxis With the House Dust Antigen. HAROLD J. FRIEDMAN, M.D. (Abstract.)

Guinea pigs were sensitized with a 1 per cent alum-precipitated house dust extract. After a sensitizing interval of from thirty to sixty days, they were tested intravenously with untreated house dust extract. Ninety-six per cent of the guinea pigs so tested showed definite signs of anaphylaxis and 80 per cent died of anaphylactic shock. Some tests for sensitivity were made with the Dale technique. In some guinea pigs the two-stage operation of Walzer and Grove was employed, not only to demonstrate hypersensitiveness but also desensitization in vivo. Of 20 guinea pigs tested with the usual Dale technique, 18 gave positive results. There were 12 intestinal or uterine strips tested by the two-stage technique. Eleven of the strips removed before the intravenous shocking dose was administered gave positive reactions at the first addition of extract to the bath. After changing the bath, restimulation with the same dose of antigen failed to produce a contraction in all but one, thus demonstrating desensitization in vitro. Of the 12 strips

removed after the animal had died of anaphylactic shock, only 2 responded to the addition of house dust to the Dale bath, but all responded to histamine stimulation. Thus desensitization in vivo was demonstrated in 10 instances.

Anaphylactic death could not be induced with intravenous injections of less than 0.1 c.c. of the house dust extract. Anaphylactoid reactions frequently occurred when doses of more than 1 c.c. were given intravenously.

The above results demonstrate that guinea pigs could be sensitized with alum-precipitated house dust extract. The specificity of the sensitivity was demonstrated by Dale tests and by neutralization of the sensitivity in vivo and in vitro with the offending antigen. The narrow working range between the minimal shocking dose and that which induces nonspecific anaphylactoid reactions is a serious handicap in the application of the above technique to investigations into the nature of the dust antigen.

Contact Reactions With Proteins in Various Atopic Illnesses. MURRAY ALBERT, M.D., and MATTHEW WALZER, M.D. (Abstract.)

In a previous communication an unusual type of contact reaction obtained with oil-free silk was reported, occurring almost exclusively in atopic children. The sensitivity was specific, nonreaginic, and could be induced by contact.

Oil-free preparations of corn, cottonseed, cow epithelium, eggs, duck and goose feathers, flaxseed, goat hair, milk, orris root, plantain, timothy and ragweed pollens, tobacco, and wool were prepared in the form of 25 per cent petrolatum ointments and were employed for patch testing. The incidence of contact reactions to feathers among atopic children was 48.3 per cent, practically the same as that to silk (48.8 per cent). Positive reactions were obtained less frequently to the remainder of the above allergens, except egg, milk, flaxseed, and plantain which gave no positive reactions.

Among 28 children with asthma, 75 per cent showed positive contact reaction to one or more of the allergens. Of 20 children with hay fever, 60 per cent reacted positively. Of 16 children with eczema and neurodermatitis, 62.5 per cent showed positive contact reactions. Twelve of 16 patients with vernal catarrh showed positive contact reactions. The atopic nature of this illness seems, therefore, to be definitely established in this manner.

Atopic adults and nonatopic children and adults showed a very much lower incidence of reactions than do atopic children. Most positive reactions occurred in atopic children between the ages of 5 and 12 years. The most severe reactions also occurred in this age group. Multiple sensitivities were common. The incidence of positive reactions was no greater in atopic illness with cutaneous symptoms than in those conditions in which the skin was unaffected.

Annual Review

ALLERGY IN DERMATOLOGY

A Critical Review of Recent Contributions*

Joseph Goodman, M.D., Boston, Mass., and
Marion B. Sulzberger, M.D., New York, N. Y.

THE work of the past year indicates a continuing interest both in the theoretical and in the practical problems of contact type of eczematous dermatitis. From the theoretical standpoint the differences in the sensitizing capacity of various simple chemicals is of considerable importance in the study of the mechanism of epidermal sensitization. Landsteiner and Di Somma[1] have studied the effect of the application to the skin of human beings and of laboratory animals of two simple chemicals, diazomethane and mustard oil. The first chemical, after repeated applications to the skin of guinea pigs, produced a moderate degree of hypersensitivity, demonstrated by reapplication to the skin. The second failed to sensitize guinea pigs, rabbits, or monkeys when applied to the skin. However, it was possible to produce hypersensitivity to mustard oil in 2 of 3 young hogs and in 1 of 6 human beings. The authors concluded that these observations "indicate species and individual differences as regards the ability to become sensitized to various chemical compounds." Clinical observation of patients with contact-type dermatitis has borne evidence of the great variability in the individual susceptibility to sensitization with different simple chemical substances.

But species and individual differences are not the only variants in contact-type dermatitis. Landsteiner and Jacobs[2] (see review of 1937) studied the sensitizing capacities in animals of several closely related chemicals. Sulzberger and Baer[3] have extended these studies to human beings, confirming the finding that trinitrobenzenes, chlordinitrobenzenes, and dichlornitrobenzenes, dropped on normal skin, vary considerably in their sensitizing effect. As in animals, the *capacity for the production of sensitization varied roughly with the alkali lability and the combining power of the compounds studied.*

Variations between individuals and related chemicals might be a manifestation of only one variable factor. However, the observations of Landsteiner, Rostenberg, and Sulzberger[4] indicate that at least *two factors* act as determinants of sensitization. If a group of normal in-

*From the Department of Dermatology and Syphilology, Massachusetts General Hospital and Harvard Medical School, and the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University.

dividuals are sensitized simultaneously with two unrelated chemical compounds, some individuals are sensitized to one substance, others to another, and some to both. Even among those sensitized to both, there are some who develop a much greater sensitivity either to one or to the other chemical. It seems likely, therefore, that there is some *individual* factor which determines the degree of susceptibility to sensitization to each particular substance, and which varies from person to person, or from animal to animal.

The knowledge that the problem of eczematous sensitization is complicated by various individual and chemical factors gives added interest to all attempts to produce artificial sensitization in man or in animals. Among other recent studies of this problem is that of Burckhardt,[5] who found that guinea pigs could be sensitized to a turpentine fraction merely by application of the substance to the skin. However, a *greater degree of sensitization was achieved if the turpentine fraction was applied with soap.* Presumably the damage to the skin produced by the alkaline soap was a factor in enhancing sensitization. Likewise a greater degree of sensitization was achieved if *aged* turpentine, containing irritating oxidation products, was used.

This study concerns itself with a problem which is clinically as well as theoretically important. It is generally conceded that various skin diseases, such as seborrheic dermatitis and fungous infections, are factors which predispose to sensitization. However, experimental studies of this aspect of contact-type dermatitis are few.

Another experimental problem in the investigation of eczematous dermatitis concerns the form of the substance with which sensitization is attempted. Helmke[6] has sensitized normal individuals to primrose by means of repeated applications of primrose leaf to the skin. The important studies of sensitivity to primrose extracts by Bloch and Steiner-Wourlisch[7] were performed in part with an extract of primrose prepared by an expensive and tedious extraction of the plant. Helmke's studies indicate that repeated applications of the whole leaf may be sufficient to replace sensitization with extracts. The primrose, like poison ivy, is a potent sensitizing agent. While it is true that the whole leaf will be sufficient for studies of experimental sensitization to such plants, it must be remembered that other plants (and many simple chemicals) are probably less active as sensitizing agents. Extraction, purification, and concentration will doubtless be necessary in the study of the sensitizing capacities of certain other plants.

A case in point is the study of Grolnick[8] who sensitized human beings experimentally to a plant, Krameria. In this instance an alcoholic extract of the plant was applied for forty-eight hours at seven- or fourteen-day intervals to the skin of 37 nonreacting individuals. Sensitivity developed in 87 per cent of this group after one to seven applications. The remainder failed to develop sensitization after seven to ten applica-

tions. It is possible that had a concentrated extract similar to that of Bloch and Steiner-Wourlisch been used, sensitization would have occurred in all the individuals of this group.

Among plants, and indeed among all causes of contact-type dermatitis in the United States, poison ivy stands out, because of the frequency with which it causes skin disease. The economic importance of poison ivy dermatitis is reflected in the number of studies of various aspects of this subject which have been published in the past year. Caulfeild[9] has presented evidence which leads him to the conclusion that a certain poison ivy extract is effective as treatment and as prophylaxis. Molitch and Poliakoff[10] have studied the effect of injections of commercial poison ivy extracts in children. Ninety per cent of one group which received two injections each of one commercial product went through four months of the spring and summer without developing a dermatitis, whereas 82 per cent of a second group which received one injection each of a second commercial extract was presumably immune by the same standards. Caulfeild's results are based on a short period of study in very few cases, and since the total number of individuals studied in the groups mentioned by the above authors was only 50, one cannot conclude that the giving of two injection treatments gave results which were superior to those achieved by a single injection.

Previous studies, especially that of Blank and Coca,[11] have indicated that injections of poison ivy extracts are effective as a prophylactic. More recently, Bachmann[12] has been unable to demonstrate immunity as a result of such injections. Moreover, Sompeyrac[13] has been unable to note any effect of such injections on patch tests with alcoholic extracts of poison ivy.

These divergent results may perhaps be reconciled by taking cognizance of several variables in contact-type dermatitis. First, it is to be expected that there will be individual differences—which should be minimized in large groups. Second, the potency of the extract must be considered; and in this connection it must be remembered that no standard of potency is available. Third, the degree of clinical exposure should be borne in mind. It is to be expected that after the injection of poison ivy antigen, certain individuals might develop sufficient protection for relatively minimal clinical exposure, but insufficient desensitization to protect against the rather massive exposures via the patch test with extracts or with whole leaf. The negative results reported by Sompeyrac[13] would be more conclusive if they were supported by studies of patch test reactions to graduated dilutions of the excitant before and after the immunizing procedure.

In unpublished studies Green and one of us (with the assistance of E. Mallozzi) performed quantitative serial patch tests before and after administering intramuscular injections of a commercial poison ivy extract. These studies, performed on approximately 119 individuals, did

not succeed in demonstrating any reduction of the level of the sensitivity of the skins to ivy extracts following the injections.

Dermatitis caused by citrus fruits has been discussed by Beerman, Fondé, and Calloway,[14] who reported 2 patients, one with a dermatitis caused by handling oranges and showing a positive patch test to orange peel, the other presenting an eczematous eruption on the face accompanied by a positive patch test to orange juice. Schwartz[15] has published an excellent summary of the cutaneous hazards present in the citrus fruit industry, emphasizing the fact that there are relatively few instances reported of dermatitis caused by citrus fruit which could be traced to dye, wax, or any other substance added to the fruit during processing. More important in the citrus fruit industry are the many instances of paronychia and of dermatitis caused by the oils of rinds of citrus fruits. Men engaged in peeling and reaming citrus fruits are particularly likely to develop these occupational diseases. Schwartz's review is highly recommended to all who are interested in the cutaneous hazards of this industry.

From the standpoint of industrial hazards the paper of Rundberg[16] is of considerable interest. One hundred painters were patch tested with four varieties of turpentine. French turpentine produced many fewer reactions than Swedish turpentine. Rundberg believes that this difference exists because French turpentine is more purified than the Swedish variety. In the light of Burckhardt's experimental work[5] already mentioned, this seems a likely explanation.

During the past year several general papers on occupational dermatitis have appeared.[17] Especially valuable is the recent review by Downing[18] of over 1,000 cases of occupational skin disease.

Thomas[19] has reviewed a series of cases of industrial dermatitis from the standpoint of the duration of sensitivity and has come to the conclusion that allergic hypersensitivity of the contact type, once established, usually is permanent. Moreover, his analysis indicates that there is a decided tendency for the hypersensitivity to spread and to include substances apparently unrelated to the original sensitizing agent.

The views expressed by Thomas as a result of his studies are those commonly held by most dermatologists. Experimentally they have been supported by the work of Burckhardt[5] who found that guinea pigs, sensitized to turpentine fractions, were still hypersensitive when retested after two and one-half years (3 out of 3 animals). It is of considerable importance that a contradiction of these views has recently come from the dermatologic clinic of the University of Zurich. First Gomez-Orbaneja and Barrientos[20] did follow-up studies on 139 patients with contact-type dermatitis. In each case the original cause of the dermatitis had been identified by means of a positive patch test. In the group of patients who succeeded in avoiding all contact with the allergen responsible for the dermatitis, there was a complete clinical cure in 74 per

cent. On the other hand, when the allergen was not eliminated, there was a cure in only 25 per cent. One hundred and six of the 139 patients were retested with the allergen which had originally produced the positive patch test. In the group of patients who avoided re-exposure, the hypersensitivity had disappeared in 61 per cent. When re-exposure had not been avoided, the hypersensitivity disappeared in only 11 per cent.

In the same clinic Miescher[21] has extended this study with a group of 86 patients with contact-type dermatitis. Of the group that avoided further contact with the allergen after its identification, 91 per cent had no further skin disease. On the other hand, none of the group that continued to come in contact with the allergen was free from eczema. When retested after an interval of two to three and one-half years, 33 of 48 patients in whom further contact with the allergen was avoided presented negative patch tests, indicating that the hypersensitivity had disappeared. On the other hand, in only 3 of 20 patients in whom such contact was not avoided had the patch test reaction disappeared. In the other 17 patients the patch test reaction was as strong as the original test, and in some instances stronger.

Substantiation of these figures is certainly indicated for they run more or less contrary to the views of most dermatologists. If confirmation is forthcoming, an important advance will have been made in our knowledge of eczematous dermatitis. At the present time the patient with contact-type dermatitis must be told that his sensitivity will probably persist indefinitely. It will certainly be heartening both to the patient and to the physician to know that strict avoidance of the allergen may result after a few years in complete disappearance of the hypersensitivity.

Among the more unusual instances of contact-type dermatitis reported during the past year is that of Kirby-Smith[22] to the mango. It is interesting to note that accompanying the dermatitis and cheilitis produced by contact with the mango rind, stems, or sap, there are often stomatitis and gastrointestinal symptoms. Of 35 volunteers tested with juice expressed from the fruit, 5 showed an erythematous and vesicular reaction.

Also unusual is the report by Newman[23] of dermatitis of the lips and fingers produced by hypersensitivity to diethylene glycol in cigarettes. One of us (M. B. S.) tested a large group of smokers with patch tests with diethyleneglycol; there were no reactions even to high concentrations. This compound is evidently nonirritating. Newman's case obviously represents an unusual but true allergic eczematous hypersensitivity.

Likewise of interest are the reports by Smith and Hughes[24] of contact dermatitis caused by the Mexican rubber plant, by Rowe[25] of contact dermatitis produced by cocklebur, and of Parkhurst and Lukens[26] of dermatitis produced by butyn.

These few instances are sufficient to indicate that the list of substances which may cause contact dermatitis is rapidly growing. Genner and Bonnevie[27] extend it further in a direction which has been little explored by their report of 2 cases of contact dermatitis produced by leaves of the elm and one by the leaf of the magnolia. It is possible that many unexplained instances of contact dermatitis may belong in this group.

Since instances of dye dermatitis are not infrequently misdiagnosed, it is worthy of mention that further cases of lipstick dermatitis have been reported by Flandin, Rabeau and Ukrainczyk,[28] by Hellier,[29] and by Sulzberger[30]; of eczema from clothing by Burgess[31] and by Tobias[32]; and of dermatitis from shoe leather and shoe polish by Lord and Wolfe.[33] Other reports that are of interest because of the rarity with which instances are met are those of Cole and Driver[34] of stomatitis and cheilitis due to dental plates, of Traub and Holmes[35] of dermatitis and stomatitis from the mercury of amalgam fillings, and of Simon[36] of a dermatitis of the fingers produced by organ keys made from a formaldehyde plastic (galalith).

The report by Hollander[37] of dermatitis produced by petrolatum brings to mind the frequency with which dermatologists meet with patients whose skin lesions do not do well with petrolatum ointments. For the most part one cannot prove that such patients are allergically hypersensitive to this substance. Patch tests in our experience are almost always negative. In the case reported by Hollander there was no doubt that petrolatum made the patient's dermatitis worse. The sensitivity of this individual was tested by rubbing petrolatum repeatedly into one skin site. The result was an eczematous reaction. However, since the results of the usual forty-eight-hour patch test are not given, it seems to us that this case cannot be accepted without reservation as one of true allergic hypersensitivity.

Several general considerations of the value of the patch test have appeared during the past year. Bonnevie[38] has pointed out the frequency with which falsely positive patch tests are found during the acute stages of a contact-type dermatitis. He has emphasized the fact that the greatest value of the patch test lies in uncovering the specific cause of the patient's eczematous dermatitis. The test is of decidedly less value as an aid to classification of the patient's dermatosis. In the course of his discussion Bonnevie takes issue with the statement of Bloch, that the eczema patient shows seven times as many patch test reactions as the normal. This finding is due to the use of an irritating concentration of turpentine and indicates only, according to Bonnevie, that the eczema patient is less resistant to toxic substances than the normal.

Schmidt[39] reports the results of patch tests on 136 patients with occupational dermatitis. In 37.5 per cent of the patients a positive reaction was found. Of 6 patients with dermatitis produced by clothes, flowers, or cosmetics, only one showed a positive patch test reaction.

Without seeing such cases personally we feel that the percentage of reactors in the occupational group cannot be evaluated properly, because of the difficulty in *differentiating between allergic and nonallergic occupational dermatitis.* The percentage of positive reactions in the small second group of 6 seems to us to be low for such cases.

Lomholt[40] has published his results in the routine patch testing of a series of 1,285 patients with allergic contact dermatitis. The details of these reactions are too complex to be summarized here. An excellent general summary of the modern conceptions and treatment of eczema is presented by Wise and Wolf.[41] We cannot subscribe to the theory put forth by Edel[42] that eczema is generally parasitic (infectious) in origin.

There remain for consideration in this section of the review two disease categories which at times have been thought to be pathogenetically related to allergic contact-type dermatitis, namely, light sensitivity produced by contact with plants, and cement eczema. Evidence is accumulating that both are not based on allergic mechanisms.

Kuske[43] has been able to produce extracts from certain plants which on the first application regularly produce skin reactions subsequent to exposure to ultraviolet light. He has, moreover, been able to isolate two relatively simple substances (bergapten from oil of bergamot and oxypeucedanin from the root of *Peucedanum ostruthium*) which regularly photosensitize on the first application. Foerster and Schwartz[44] have recently studied industrial dermatitis and melanosis due to photosensitization in workers handling pitch or pitch products. Their conclusion was that these conditions were not produced by an allergic contact type of hypersensitivity.

Cement eczema has been the subject of a careful study by Burckhardt.[45] Eighty patients with cement eczema and 100 control patients were studied by means of patch tests to cements and various components of cements. In general, the eczema group showed reactions to lower concentrations of the substances investigated (lower threshold of reaction) than did the control group. The lowered threshold of reaction was found to run *parallel with the ability of the individual's skin to neutralize alkali.* In only one of the 80 cement-eczema patients was there reliable evidence of an allergic contact-type sensitivity. The author's conclusions, which are well documented by information which is not reproduced here, are that exposure to cement produces eczema in those individuals whose skins neutralize alkali slowly; that the exposure to alkali is the main factor in the production of the eczema; but that in all likelihood the calcium in itself plays a part. Cement eczema, therefore, is not generally an allergic contact-type dermatitis. An excellent discussion of the clinical aspects of cement eczema concludes one of Burckhardt's papers.[45b]

ATOPIC DERMATITIS

The reliability of the skin reactions in infantile eczema has been doubted by many observers. Therefore, any information which supports the significance and the specificity of reactions in the infants' skin is welcome. The recent study of Pacheco[46] of the skin reactions of infants to a filtrate of a bouillon culture of colon bacillus again confirms the specificity of these reactions. Breast-fed infants with *no colon bacilli in the stools gave negative reactions. Bottle-fed infants and infants on mixed diets, whose stools contained colon bacilli, gave positive reactions in all instances.*

This study clearly reveals the specificity of the skin reaction to colon bacillus extracts. On the whole, the evidence now seems adequate to permit the conclusion that skin reactions, or the absence of skin reactions, in the infant may be evaluated more or less on the same basis as in the adult. Positive reactions usually mean previous exposure and specific skin sensitization.

The studies of Hill[47] of skin reactions of infants to intradermal tests have revealed frequent positive tests to eggs, wheat, and milk, and less frequent reactions to other foods and to environmental allergens. These findings have led this investigator to the conclusion that foods, and especially milk, play a very important role in causing infantile eczema.

Osborne and Walker[48] presented a study of the role of contact and environmental allergens in infantile eczema. Their conclusion, after a careful study of a large series of patients, is that contact and environmental allergens are more important in this group than are food allergens. Foods, they found, were of importance in not more than 15 or 20 per cent of the cases of eczema in infants or children. These findings are not in entire agreement with the findings of Hill. However, the difference between the results of Osborne and Walker, on the one hand, and Hill, on the other, are more apparent than real, for both recognize the truth of the proposition emphasized by Peck and by Sulzberger, namely, that external, inhalant, and food allergens all play a part in infantile eczema. The difference in emphasis placed by these observers on the various routes of exposure to allergens may well depend on differences in the disease process itself from city to city.

We do not agree with the conclusions of Osborne and Walker that the use of ammoniated mercury on the skins of infants is a factor in broadening the base of their allergy. Further evidence on this point seems necessary. True allergic contact dermatitis is extremely rare in the infant, even from ammoniated mercury. Granted that eczematogenous contact substances play an important role in infantile eczema, we believe that the eruptions so produced have little, if any, relationship to adult allergic contact-type dermatitis. We are inclined to look upon such infantile eruptions either as nonspecific irritation of clinically or

subclinically diseased skin, or as a true allergic reaction of the urticarial type, produced by penetration of allergens through the skin to the blood vessels (transepidermal penetration). In other words, these reactions are not, in our opinion, comparable to allergic contact-type dermatitis. Ratner,[49] in a review of a large series of children with various allergic diseases, also points out the importance of the external exposures in infantile eczemas.

The value of the leucopenic index in the investigation of allergic diseases has been subjected to statistical analysis by two groups of observers.[50] Both have come to the conclusion that the method is of little value. Indeed, no reliable evidence could be adduced by these investigators for the existence even of a normal leucocytosis following the ingestion of food.

The problem of the distribution of the lesions of atopic dermatitis has been studied by Williams.[51] The intramuscular injection of histamine in normal individuals is usually followed by a rise in skin temperature on the face and neck. In patients with atopic dermatitis it was found that this rise in skin temperature was not limited to the face and neck, but also occurred in the other areas in which this skin disease appears. This study is a renewed attempt to investigate problems relating to the localization of skin diseases. There is need for considerable work in this subject in relation not only to atopic dermatitis but also to many other dermatoses.

Knowles and others[52] have again analyzed the reaction to patch tests with poison ivy extracts of atopic and nonatopic individuals. Their findings confirm those of previous investigators (Coca and Milford). Sensitivity to poison ivy occurs with approximately equal frequency in the two groups. The results of this study lay emphasis on a problem which is of considerable theoretical importance. The work of Landsteiner and his collaborators (previously discussed and in last year's review) tends to minimize the theoretical differences between contact (epidermal) and atopic (vascular) allergy. From the clinical standpoint, however, it is difficult to uncover points of relationship. Both remain distinct disease processes, related only by the fact that each is dependent on the patient's altered capacity to react to various allergens. In the one case the alteration is in the blood vessels; in the other, perhaps pre-eminently in the epidermis. In the first instance there is a familial tendency to become sensitive; in the second no familial tendency has been demonstrated. This difference has been more fully discussed in previous reviews.

URTICARIA AND URTICARIAL REACTIONS TO SKIN TESTS

Urbach's[53] review of 500 patients with urticaria illustrates well the multiplicity of the problems which await solution in this field. Of this group, only 110 could be classified definitely as allergic. Food allergy could be demonstrated in approximately 20 per cent of the patients; 58

per cent of the patients were apparently cured, while 15 per cent of the patients were uninfluenced by treatment of various sorts.

It becomes apparent from such figures that the syndrome of urticaria comprises various disease entities, probably differing in pathogenesis. Some are allergic, others are not. Waldbott and Ascher[54] have described urticaria of the serum sickness type. Descriptions of other varieties might well be added. Further study of Walzer's[55] recently described "new immunologic wheal produced experimentally by reverse technic" may well throw some light on certain of the clinical puzzles presented by the urticarias.

The effect of heat, cold, and psychic stimuli has been discussed by Hopkins, Kesten, and Hazel,[56] who distinguish two types of urticaria from heat: the localized type in which the wheals result from the direct action of heat on the skin, and the generalized type in which the wheals are probably produced by the action of acetylcholine on certain cells of the skin. Generalized urticaria from cold is believed to be based on a similar mechanism, while localized cold urticaria may be due to the presence of an autoantibody which reacts only at low temperatures.

Vitamin C deficiency as a cause of urticaria has been reported by Rosenberg.[57] We believe, however, that the case for vitamin C deficiency has not been proved. Many urticarias are acute and self-limited. The finding of cure after the administration of vitamin C cannot be accepted without further evidence. The same comment is pertinent in regard to the report of Caven[58] on the cure of urticaria with small doses of insulin.

Considerable interest has been aroused recently in the treatment of urticaria with potassium salts, with or without a low sodium intake.[59] Here again we meet with considerable difficulty in evaluating results, for the cure may be spontaneous. If further study proves the effectiveness of this mode of treatment, it must be remembered that its mechanism doubtless is not specific.

DRUG ERUPTIONS

The problems of experimental arsphenamine hypersensitivity have continued to attract considerable attention during the past year. Frei and one of us (M. B. S.)[60] reported experiments on guinea pigs sensitized to old arsphenamine. It was found that after such sensitization, the intravenous injection of old arsphenamine plus homologous serum usually resulted in anaphylactic shock, whereas the intracardiac injection of the same mixture into similarly sensitized guinea pigs only rarely gave this result. In addition it was found that, although sensitization to old arsphenamine regularly produced strong skin reactions to neoarsphenamine, the intravenous injection of neoarsphenamine plus homologous serum did not result in anaphylactic shock. Old arsphenamine occupies a unique position in being a simple chemical capable of producing (1) anaphylactic sensitization, (2) skin sensitization, and (3) anaphylactic shock.

It is difficult to interpret these findings at the present time, unless we assume that in the guinea pig there are two varieties of sensitization to the arsphenamines, perhaps fundamentally but not entirely related. The whole problem of experimental sensitization in animals is complicated by the existence of several types of sensitization. Progress in this field is necessarily slow, since one often finds that the manifestation of sensitization varies from animal to animal, from species to species, from substance to substance. Moreover, it is particularly difficult to correlate the results of animal experiments with the manifestations of sensitization in the human being. It seems unlikely, for instance, that from the standpoint of allergy the reaction in the guinea pig to the intracutaneous injection of old arsphenamine or to the intravenous injection of old arsphenamine plus homologous serum can be considered identical with arsphenamine dermatitis in the human being. In other words, the guinea pig becomes sensitive in a different manner from the human being. Each species may become sensitive in a manner peculiar to itself.

A study by Cormia[61] of the effect in the guinea pig of a streptococcus infection plus vitamin C deficiency on arsphenamine hypersensitivity is of considerable interest. It was found that in the presence of vitamin C deficiency, the streptococcus infection materially enhanced the skin reaction to arsphenamine. After the administration of vitamin C, this effect disappeared.

The relationship of acute or chronic infection to arsphenamine sensitivity in the human being has been suspected by John Stokes and other clinicians. Unfortunately, however, as we have stated, it is unwise to apply the results of such experiments directly to the human being. The statement also applies to the studies of the role of vitamin C in arsphenamine sensitization (see last year's review).

Cohen[62] has reported studies of the relationship of vitamin C to anaphylaxis and to arsphenamine sensitivity in the guinea pig. In a series of well-controlled experiments, he states that he has been unable to support the previous studies of this problem. No relationship could be demonstrated between either excess of or deficiency of vitamin C and anaphylaxis or arsphenamine hypersensitivity. Cohen makes two important criticisms of previous studies of these problems: (1) The diet was not carefully controlled and was possibly not deficient in vitamin C only. (2) The number of animals used was too small to permit reliable conclusions. However, a close analysis of Cohen's tables demonstrates that the incidence of sensitization was materially lower in the animals receiving the highest amounts of vitamin C. This result is in conformity with the previous findings of Sulzberger and Oser, Cormia, Wiedemann, and others.

To give added emphasis to the difficulty already discussed of applying to the human being the results of animal experiments, attention should be given to the experiments of Saito[63] on the human being. This in-

vestigator found that one to three applications of neoarsphenamine to the skin were sufficient to induce sensitization as evidenced by the local patch test reaction. However, no spread of sensitization beyond the original site of application could be demonstrated, nor could local or generalized manifestations be induced in the sensitized individual by intravenous injection of neoarsphenamine. These observations confirm certain of the previous studies of the patch test reaction to arsphenamines in patients who have developed exfoliative dermatitis from antisyphilitic treatment.[64] The positive patch test in patients under treatment does not always indicate danger from a continuation of treatment, nor, conversely, does a negative patch test indicate that further treatment is safe (Sulzberger and Chargin).

Skin reactions to sulfanilamide have been reported often during the past year. Reports of several varieties of such eruptions were noted in last year's review. In addition to those previously noted Saphirstein[65] has reported hepatitis and toxic erythema, and Noun[66] has studied erosions of the oral mucosa and urticaria following small doses of sulfanilamide. Of particular interest is the study by Schlesinger and Mitchell[67] of 10 patients in whom a morbilliform eruption resulted from the administration of sulfanilamide. The eruption appeared within five to seventeen days after the start of the administration of the drug. In all cases there was a short prodromal period of fever. Repeated administration of gradually increasing doses was successful in decreasing or abolishing the patients' reactions to the drug. These authors quite justly point out the similarity of this syndrome to "Nirvanol sickness." Positive patch tests were said to be present in two instances, but these were not adequately described. Loveman of Louisville has observed a case of typical fixed eruption proved due to sulfanilamide (personal communication—to be published).

Additional cases of cinchophen poisoning have been reported by Sugg.[68] The manifestations of cinchophen sensitivity are found in the skin and in the liver in Sugg's patients, in the proportion of 10 to 22. The author points out that "toxic" reactions to cinchophen do not appear after the first dose of the drug—an important point in establishing the allergic character of the reaction both in the skin and in the liver.

A lichenoid, verrucous and vegetating eruption from gold has been described recently by Pautrier and Roederer.[69] Schwatt and Rest[70] studied the patch test reaction to a gold salt in patients who had developed various complications of gold therapy. Only 25 per cent of the patients are said to have shown positive reactions. Unfortunately, the value of this study is impaired by two factors. First, the patch test was not read as positive unless frank vesiculation was present. Second, the percentage of reactions is figured on the basis of tests of patients with various complications of gold therapy (stomatitis, gastroenteritis) and not just on those showing dermatitis.

SKIN ALLERGY IN INFECTIOUS DISEASES

It was noted in last year's review that further studies of the response to injections of staphylococcus toxoid, as measured by the blood antitoxin titer, were necessary for a better evaluation of this agent. Unfortunately, the work of the past year has resulted in only one paper, by Tanenbaum and associates,[71] which deals with this subject. These investigators report a study of 100 university students with acne vulgaris, treated with staphylococcus toxoid. Cure or good improvement resulted in over half of the group. In general, the authors report better results in pustular acnes than in other varieties. They also found that the improvement did not correspond with the increase in antitoxin titer in the blood. It seemed rather that the degree of sensitivity to the toxoid, as measured by intracutaneous tests with diluted toxoid at the start of the treatment, gave a better indication of result than did the antitoxin titer.

Our experience with acnes has not been as fortunate as that of Tanenbaum and co-workers. We feel, however, that toxoid has been of some help in a few cases of cystic acne in older women. Further studies of the antitoxin titer are necessary. Some of our best results have been in patients who developed very high titers. In other cases the results were not parallel to the blood antitoxin titers.

The specific therapy of herpes simplex has been studied by Frank.[72] Formalized brain emulsions, prepared from animals infected with the virus of herpes simplex, were repeatedly injected into 14 patients who presented regularly recurring attacks of this disease. Thirteen of these patients showed considerable improvement, as indicated by the length of the interval between attacks and the severity of the individual attacks. A study of blood for neutralizing substances for herpes virus revealed no relationship to the success of the immunizing procedure. The patients who improved most had no increase in the titer of these bodies in the blood (compare our experience with staphylococcus toxoid).

This study demonstrates very well one of the most important difficulties encountered in studying the immunologic aspects of many skin diseases. In this instance, and in other diseases as well, it appears that the immunologic change which leads to cure is purely a local process, involving only that portion of the skin affected by the disease. In spite of such difficulties, however, Frank's study is of considerable interest and importance.

The use of mouse brain antigen for the Frei test, as proposed by Grace and Suskind,[73] has been the subject of two reports during the past year. Reider and Canizares[74] report favorably on its use, but emphasize the care with which reactions must be evaluated, particularly if the patient shows a reaction to the control injection of normal mouse brain. On the other hand, Binkley and Love[75] have found that the mouse brain antigen is not suitable for diagnostic use. These investigators find that

there are many reactions to normal mouse brain. In their hands these reactions caused so much difficulty in reading the results of the tests that they returned to the use of material derived from pus recovered from patients in the acute stages of the disease.

Gastinel, Pulvenis, and Collart[76] have restudied certain problems of immunity in experimental syphilis. Rabbits were infected with syphilis, treated with neoarsphenamine one hundred or more days after infection, and reinfected after one and one-half to twenty months with the same strain of spirochetes. It was found that when reinfection took place within ten months after the conclusion of treatment (24 animals), there resulted one abortive chancre and two symptomless infections. When reinfection took place ten to twenty months after treatment (9 animals), there were three typical chancres and no symptomless reinfections (as judged by node transfers).

This study demonstrated that the acquired immunity to syphilis lasted for twenty months in some animals. On the whole, however, it was less effective with the passage of time after treatment of the first infection.

Tani and Aikawa[77] have reported studies of a similar problem, but their work merely confirms that of Chesney,[78] in that they found evidence for the existence of immunity in animals treated one hundred or more days after infection, and then reinfected with the same strain of spirochetes.

The relationship of the eye to immunity in experimental syphilis has been reported on by Chesney, Woods, and Campbell.[79] In a long series of experiments, to summarize the results as briefly as possible, it was found that the eye does not participate as much as other tissues in the development of resistance to syphilis and that there was "no need and indeed no ground for invoking a state of allergy to explain [these] findings in rabbits."

TRICHOPHYTIN AND TUBERCULIN ALLERGY

Lewis, MacKee, and Hopper[80] report the results of an extensive study of reactions to trichophytin. For the purpose of determining the specificity of this test, the authors present tables which compare skin reactions to trichophytin, oidiomycin, and catarrhal vaccine. These tests were performed on 25 patients from whom a trichophyton was isolated from skin lesions by culture. At forty-eight hours 22 patients showed reactions to oidiomycin, 9 to catarrhal vaccine. Likewise in 20 patients from whose skin lesions a monilia was cultured, there were 6 reactions to trichophytin and 5 to catarrhal vaccine. In a group of 25 patients with a positive intradermal test to catarrhal vaccine, there were 19 reactions to oidiomycin and 3 to trichophytin. The dissimilarity in the number and strength of the reactions to these three extracts in all three groups is strong support for the specificity of each.

Of considerable interest is a table which these investigators present showing the per cent of positive reactions to trichophytin in patients who present fungous infections, proved culturally. Of 39 patients with *Microsporon lanosum* infections, 76 per cent showed positive trichophytin tests, whereas of 48 patients with *Microsporon audouini* infections only 31 per cent showed positive tests. Of the group of patients with *Trichophyton gypseum* infections, 71 per cent showed positive tests, while only 24 per cent of those infected with *Trichophyton purpureum* were positive. It was found also that when *Trichophyton gypseum* could be cultured from foot lesions, there were almost 60 per cent to 70 per cent positive trichophytin reactions; when, however, the culturally positive foot lesions were accompanied by hand lesions, the per cent of positive tests rose to about 90. These findings again illustrate the close interrelationship between species of fungus (animal or human types); capacity to produce skin sensitivity; form and course of disease; and response to therapy, as well as tendency to spontaneous cure. (For the earlier work and further details on this subject see the review by Wise and Sulzberger, *The Year Book of Dermatology and Syphilology*, 1938.)

A further point of interest was the finding of about 20 per cent positive tests to trichophytin in patients under 20 with skin diseases not caused by fungi, as compared to over 30 per cent positive reactions in a similar group over 50 years of age. Thus the positive trichophytin test, like the positive tuberculin test, is a manifestation of past infection as well as of present infection. The interpretation of the positive trichophytin test and the limitations of the test are the same as for the tuberculin test.

While studies of reactions to fungous extracts have been very few during the past year, much attention has been paid to tests with old tuberculin and other products of the tubercle bacillus. Sabin[81] has studied in guinea pigs the cellular reaction produced by intradermal and intraperitoneal injection of tuberculophosphatide and of so-called waxes prepared from the tubercle bacillus. There resulted first the formation of monocytes, then fusion of monocytes to form foreign body giant cells, and lastly disintegration of the lipid material in the giant cells. Similar injections of tuberculoproteins, on the other hand, produced much more complex reactions, consisting of monocytes, macrophages, epithelioid cells, single and in tubercles, and giant cells of the Langhans and foreign body types.

A comparison of the cellular reaction to these products in normal and in tuberculous animals revealed the following: tuberculoprotein in solution induced the formation of monocytes in the normal animal, and epithelioid cell tubercles in the tuberculous animal. Freshly precipitated tuberculoprotein induced the formation of epithelioid cells both in the normal and in the tuberculous animal. However, the epithelioid cells were more numerous in the tuberculous animals. Insoluble forms of

tuberculoprotein induced the formation of complex tubercular tissue both in normal and in tuberculous animals, but the reaction was more marked in the latter.

In a similar manner Sabin and Joyner[82] studied cellular reactions to defatted tubercle bacilli and their products. Again it was found that various fractions produced varying reactions.

These analyses of reactions to products of the tubercle bacillus, by intradermal and intraperitoneal injection into the guinea pig, furnish another demonstration of the complexity of the antigenic composition of microorganisms. Jadassohn and his co-workers[83] have previously analyzed complex antigens (trichophytins and tuberculins) by means of the Schultz-Dale technique (see last year's review). On the whole, this work is not far enough advanced at present to permit practical application. However, continued study of these phenomena will certainly lead to results of great theoretical and practical importance, for example, the recognition and possible application of the synergistic effects of the various chemical fractions of microorganisms.

Cooper and Cohn[84] have studied in guinea pigs certain aspects of immunity and allergy in relation to tuberculoproteins. They found that a specific immunity against infections with virulent human tubercle bacilli could not be produced by the intracutaneous or subcutaneous injection of filtrates from cultures of tubercle bacilli, by concentrated filtrates, by precipitated tuberculoprotein or by alum-treated filtrates. Intravenous injection of these substances also failed to produce an immunologic alteration that would be disclosed by a subsequent intracutaneous test with the substance first injected. However, a second intravenous injection of the same substance in each instance produced an anaphylactic shock. Cutaneous hypersensitivity to tuberculoprotein could be produced only by infection with small amounts of living, avirulent human tubercle bacilli; with still smaller amounts of living, virulent human tubercle bacilli; or with a very large dose of heat-killed tubercle bacilli. This study again brings out quite clearly the antigenic complexity of the tubercle bacillus. As the authors point out, immunity and specific sensitivity are two closely related factors which show striking quantitative differences, but whether they are derived from the same or different fractions of the tubercle bacillus must be left for the future to disclose.

The experimental work of Birkhaug[85] has led him also to consider specific sensitivity and immunity to be relatively separate processes in tuberculosis. This investigator has found that, while there was a general spread of tubercle bacilli within three days after injection in the normal animal, the same spread occurred only after 5 weeks in the allergic, tuberculin-sensitive animal, and only after 7 weeks in the animal desensitized to tuberculin. The fact that the desensitized animal shows

slower spread than the hypersensitive animal demonstrates, according to Birkhaug, that sensitivity and acquired specific immunity are separate processes.

Willis and Woodruff,[86] on the other hand, reach a different conclusion with a somewhat similar experiment that differs from that of Birkhaug in being carried out for a longer period of time. Desensitized guinea pigs at first showed a good immunity to tuberculosis, but after months they lost that immunity. In fact, the specifically sensitive but not desensitized control group handled the infection better than the group of desensitized animals. The authors conclude that specific sensitivity itself plays a part in the immune process.

The problem of sensitization was discussed in the first review of this series (May, 1936). It seems to us that in spite of the work just discussed and in spite of much work done in previous years, this problem is far from being settled. The middle ground seems safest for the present: Specific sensitivity and specific resistance need not be entirely identified one with the other nor entirely separated from one another. Each is a part of related specific biologic processes. There is greater or less divergence of the two at various points, but some fundamental undeniable relationship remains.

McCarter, Getz, and Stiehm[87] have studied in man the reactions to intracutaneous injections of purified protein derivatives of human, bovine, and avian tubercle bacilli and to smegma bacilli. Although certain crossed reactions occurred, it was found that in general human and bovine tubercle bacilli were closely related and produced more or less the same skin reactions. The avian and smegma preparations, however, each showed very little relationship to the human and bovine preparations.

Vollmer and Goldberger[88] have compared the tuberculin patch test and the Mantoux test with purified protein derivative in 169 tuberculous children. One hundred and sixty-four reacted positively to both. One subject was negative by the intradermal test, but positive by the patch test. The remaining 4 were negative to both. Intradermal tests with the second strength of purified protein derivative were done in these 4 patients. Two were again negative. The other 2 showed positive reactions, and a repeat of the patch test was positive in one of these 2. In only one instance, therefore, was there a positive intradermal test accompanied by a negative patch test. Of 118 children admitted to a pediatric ward, 12 showed positive patch tests to tuberculin. Eight of these had positive Pirquet tests, 2 had questionably positive Pirquet tests, and 2 had negative Pirquet but positive Mantoux tests.

The results of this study certainly speak for a close correlation between the Mantoux and the tuberculin patch test. However, we are of the opinion that further studies are required as to the significance of the patch test reactions, and particularly as to whether all the patch test

reactions are fundamentally the same. The reasons for this attitude are given in last year's review and need not be repeated here.

In concluding this review, we again apologize for omissions, both of papers overlooked and of papers which for lack of space could not be discussed. The material published during the past year has been large. The greatest progress during the year has been in studies of eczematous contact-type dermatitis and of sensitivity to simple compounds; in extension of knowledge regarding the complex nature of the extracts of infectious microorganisms, and the individual and synergistic effects of their various chemical fractions.

REFERENCES

1. Landsteiner, K., and Di Somma, A. A.: Studies on the Sensitization of Animals With Simple Chemical Compounds. V. Sensitization to Diazomethane and Mustard Oil, J. Exper. Med. **68**: 505, 1938.
2. Landsteiner, K., and Jacobs, J.: Studies on the Sensitization of Animals With Simple Chemical Compounds. II. J. Exper. Med. **64**: 625, 1936.
3. Sulzberger, M. B., and Baer, R. L.: Sensitization to Simple Chemicals. III. The Relationship Between Chemical Structure and Properties, and Sensitizing Capacities in the Production of Eczematous Sensitivity in Man, J. Invest. Dermat. **1**: 45, 1938.
4. Landsteiner, K., Rostenberg, A., and Sulzberger, M. B.: Individual Differences in Susceptibility to Eczematous Sensitization With Simple Chemical Substances, J. Invest. Dermat. **2**: 25, 1939.
5. Burckhardt, W.: Experimenteller Sensibilisierung des Meerschweinchens gegen Turpentinöl (Pinen), Acta dermat. venereol. **19**: 359, 1938.
6. Helmke, R.: Ueber die willkürliche Erzeugung der Primel-empfindlichkeit an Haut und Schleimhaut, Med. Klin. **2**: 1303, 1937.
7. Bloch, B., and Steiner-Wourlisch, A.: Die willkürliche Erzeugung der Primelüberempfindlichkeit beim Menschen und ihre Bedeutung für das Idiosynkrasieproblem, Arch. f. Dermat. u. Syph. **152**: 283, 1926.
8. Grolnick, M.: Studies in Contact Dermatitis. III. Active Sensitization Induced With Krameria, J. Invest. Dermat. **1**: 179, 1938.
9. Caulfeild, A. H. W.: The Specific Diagnosis and Treatment of Poison Ivy (Rhus Toxicodendron) Dermatitis, J. ALLERGY **9**: 535, 1938.
10. Molitch, M., and Poliakoff, S.: Prevention of Dermatitis Venenata Due to Poison Ivy in Children. A Comparison of the Single and Multiple Injection Methods, J. ALLERGY **9**: 270, 1938.
11. Blank, J. M., and Coca, A. F.: Study of the Prophylactic Action of an Extract of Poison Ivy in the Control of Rhus Dermatitis, J. ALLERGY **7**: 552, 1936.
12. Bachmann, L. C.: Prophylaxis of Poison Ivy. Use of an Almond Oil Extract in Children, J. Pediat. **12**: 31, 1938.
13. Sompeyrac, L. McC.: Negative Results of Rhus Antigen Treatment of Experimental Ivy Poisoning, Am. J. M. Sc. **195**: 361, 1938.
14. Beerman, H., Fondé, G. H., and Callaway, J. L.: Citrus Fruit Dermatoses, Arch. Dermat. & Syph. **38**: 225, 1938.
15. Schwartz, L.: Cutaneous Hazards in the Citrus Fruit Industry. Brief History of Citrus Fruit in Florida and in California, Arch. Dermat. & Syph. **37**: 631, 1938.
16. Rundberg, G.: Terpentinekzem bei schwedischen Malern. Eine gewerbehygienische Untersuchung, Hygiea **99**: 209, 1938.
17. Blaisdell, J. H.: Medicolegal Complications in Dermatology Caused by Massachusetts Workmen's Compensation Act, Arch. Dermat. & Syph. **39**: 69, 1939.
Gillespie, R. D.: Industrial Dermatitis and the Workmen's Compensation Act, Brit. J. Dermat. **49**: 422, 1937.
Hill, A. G. E.: Industrial Dermatitis From the Legal Standpoint, Brit. J. Dermat. **49**: 427, 1937.
Holtzmann, F.: Zur Frage der Anerkennung von Hautekzemen als Berufskrankheit, Zentralbl f. Gewerbehyg. **14**: 234, 1937.
MacCormac, H.: Industrial Dermatitis and the Workmen's Compensation Act, Brit. J. Dermat. **49**: 490, 1937.
Sézary, A.: Les dermatoses professionelles, Presse méd. **2**: 1326, 1937.

18. Downing, J. G.: Cutaneous Eruptions Among Industrial Workers: A Review of Two Thousand Claims for Compensation, Arch. Dermat. & Syph. **39**: 12, 1939.
19. Thomas, E. W.: An Inquiry Into the Prognosis in Occupational Dermatitis, St. Thomas's Hosp. Rep. **2**: 24, 1937.
20. Gomez-Orbaneja, J., and Barrientos, E.: Funktionelle Nachuntersuchungen bei Ekzematikern, Schweiz. med. Wchnschr. **1**: 694, 1938.
21. Miescher, G.: Katamnestische Untersuchungen bei Ekzematikern, Schweiz. med. Wchnschr. **68**: 783, 1938.
22. Kirby-Smith, J. L.: Mango Dermatitis, Am. J. Trop. Med. **18**: 373, 1938.
23. Newman, B. A.: Dermatitis Caused by Diethylene Glycol in Tobacco, J. A. M. A. **111**: 25, 1938.
24. Smith, L. M., and Hughes, R. P.: Dermatitis Caused by Mexican Rubber Plant, Arch. Dermat. & Syph. **38**: 780, 1938.
25. Rowe, A. H.: Contact Allergy to Cocklebur (Xanthum Spinosum): A Preliminary Report, Arch. Dermat. & Syph. **39**: 149, 1939.
26. Parkhurst, H. J., and Lukens, J. A.: Dermatitis Due to Butyn, J. A. M. A. **112**: 837, 1939.
27. Genner, V., and Bonnevie, P.: Eczematous Eruptions Produced by Leaves of Trees and Bushes, Arch. Dermat. & Syph. **37**: 583, 1938.
28. Flandin, C., Rabeau, H., and Ukraineczyk: Un cas de cheilite par intolérance double à l'éosine et au groupe terpénique, Bull. Soc. franç. de dermat. et syph. **45**: 928, 1938.
29. Hellier, F. F.: Lipstick Dermatitis With a Report of a Case Due to Eosin, Brit. J. Dermat. **49**: 485, 1937.
30. Sulzberger, M. B.: Cheilitis (Lipstick?), Arch. Dermat. & Syph. **38**: 118, 1938.
31. Burgess, J. F.: Contact Eczema From Dyed Clothing, Canad. M. A. J. **37**: 237, 1937.
32. Tobias, N.: Dermatitis From Wearing Apparel, Internat. Clin. **3**: 130, 1938.
33. Lord, L. W., and Wolfe, W. D.: Dermatitis Due to Shoe Leather and Shoe Polish, Arch. Dermat. & Syph. **38**: 434, 1938.
34. Cole, H. N., and Driver, J. R.: Stomatitis and Cheilitis Due to Dental Plates, Arch. Dermat. & Syph. **37**: 338, 1938.
35. Traub, E. F., and Holmes, R. H.: Dermatitis and Stomatitis From the Mercury of Amalgam Fillings, Arch. Dermat. & Syph. **38**: 349, 1938.
36. Simon, C.: Dermite des doigts et onyxis provoqueés par le contact professionel de touches d'orgue en galalith, Bull. Soc. franç. de Dermat. et Syph. **45**: 614, 1938.
37. Hollander, L.: Dermatitis Produced by Petrolatum, Arch. Dermat. & Syph. **38**: 49, 1938.
38. Bonnevie, P.: Der Wert der Routinemässigen Anwendung einer Standardserie von Ekzemproben in der Hautpraxis, Arch. f. Dermat. u. Syph. **177**: 69, 1938.
39. Schmidt, U.: Erfahrungen mit der Epicutanprobe beim Ekzem, Arch. Dermat. u. Syph. **177**: 77, 1938.
40. Lomholt, S.: Ergebnisse eine Serienuntersuchung von 3,500 Ekzemkranken mittels Testproben, Arch. f. Dermat. u. Syph. **17**: 65, 1938.
41. Wise, R., and Wolf, J.: Eczema, J. A. M. A. **111**: 2106, 1938.
42. Edel, K.: Die Ursache des Ekzems, Acta dermat. venereol. **19**: 220, 1938.
43. Kuske, Hans: Experimentelle Untersuchungen zur Photosensibilisierung der Haut durch pflanzliche Wirkstoffe; Lichtsensibilisierung durch Furocumarine als Ursache verschiedener phytogener Dermatosen, Arch. f. Dermat. u. Syph. **178**: 112, 1938.
44. Foerster, H. R., and Schwartz, L.: Industrial Dermatitis and Melanosis Due to Photosensitization, Arch. Dermat. & Syph. **39**: 55, 1939.
45. (a) Burckhardt, W.: Des Zementekzem, Schweiz. med. Wchnschr. **1**: 738, 1938.
(b) Burckhardt, W.: Das Maurerekzem (Eine experimentelle und klinische studie zur Ekzemfrage), Arch. f. Dermat. u. Syph. **178**: 1, 1938.
46. Pacheco, G.: Sur l'allergie cutanée produite par les filtrats de culture de colibacilles, Compt. rend. Soc. de biol. **128**: 220, 1938.
47. Hill, L. W.: Sensitivity to Cow's Milk in Infantile Eczema, J. Pediat. **12**: 725, 1938.
48. Osborne, E. D., and Walker, H. L.: Contact and Environmental Allergens as a Cause of Eczema in Infants and in Children, Arch. Dermat. & Syph. **38**: 511, 1938.
49. Ratner, B.: Allergy in Childhood: III. Its Onset and Natural Progress, J. A. M. A. **111**: 2345, 1938.

50. Loveless, M., Dorfman, R., and Downing, L.: A Statistical Evaluation of the Leucopenic Index in Allergy, J. ALLERGY **9**: 321, 1938.
Brown, E. A., and Wadsworth, G. P.: The Leucopenic Index, J. ALLERGY **9**: 345, 1938.
51. Williams, D. H.: Skin Temperature Reaction to Histamine in Atopic Dermatitis, J. Invest. Dermat. **1**: 119, 1938.
52. Knowles, F. C., Decker, H. B., Pratt A. G., and Clarke, J. A., Jr.: Susceptibility of Allergic and Non-Allergic Persons to Rhus Toxicodendron, Arch. Dermat. & Syph. **38**: 773, 1938.
53. Urbach, E.: Critische Uebersicht über 500 eigene Urticariafälle (Zugleich ein Beitrag zum Problem: Allergisiche oder pathergische Urticaria), München med. Wchnschr. **2**: 2054, 1937.
54. Waldbott, G. L., and Ascher, N. S.: Urticaria of the Serum Sickness Type. Report of 5 Cases, J. ALLERGY **9**: 584, 1938.
55. Walzer, A.: Urticaria. VI. A New Immunologic Wheal Produced Experimentally by Reverse Technic, Arch. Dermat. & Syph. **38**: 1, 1938.
56. Hopkins, J. G., Kesten, B. M., and Hazel, O. G.. Urticaria Provoked by Heat or by Psychic Stimuli, Arch. Dermat. & Syph. **38**: 679, 1938.
57. Rosenberg, W. A.: Vitamin C Deficiency as a Cause of Urticaria, Arch. Dermat. & Syph. **37**: 1010, 1938.
58. Caven, W. R.: The Use of Insulin in Urticaria (A Preliminary Report), Canad. M. A. J. **38**: 459, 1938.
59. Cohen, A. E.: The Treatment of Chronic Urticaria With a High Protein, Low Sodium, Acid-Ash Diet, With Added Potassium Chloride, J. ALLERGY **10**: 61, 1938.
Rusk, H. A., and Kenamore, B. D.: Urticaria. A New Therapeutic Approach, Ann. Int. Med. **11**: 1838, 1938.
60. Frei, W., and Sulzberger, M. B.: Further Studies in Arsphenamine Hypersensitiveness in Guinea Pigs. I. Cutaneous and Anaphylactic Responses to Old Arsphenamine and Neoarsphenamine After Sensitization With Old Arsphenamine, J. Invest. Dermat. **1**: 191, 1938.
61. Cormia, F. E.: Experimental Arsphenamine Sensitization. Further Observations on the Reactions to Arsphenamine in Guinea Pigs Given Staphylococcus Toxin, and in Guinea Pigs With Induced Streptococcal Infections, J. Invest. Dermat. **1**: 199, 1938.
62. Cohen, M. B.: Vitamin C Deficiency: Sensitivity to Neoarsphenamine and Anaphylactic Shock, J. ALLERGY **10**: 15, 1938.
63. Saito, H.: Experimentelle Sensibilisierung der Menschlichen Haut mit Neosalvarsan, Hihu-to-Hitunyo. **6**: 500, 1938. Summarized in Zentralbl f. Haut-u. Geschlechtskr. **61**: 294, 1939.
64. Robinson, H. M.: Patch Tests in the Determination of Arsphenamine Sensitization, South. M. J. **27**: 845, 1934.
65. Saphirstein, H.: Hepatitis and Toxic Erythema With Desquamation Due to Sulfanilamide, Urol. & Cutan. Rev. **42**: 101, 1938.
66. Noun, M. H.: Erosions of the Oral Mucosa and Urticaria of the Body Following Small Doses of Sulfanilamide, Arch. Dermat. & Syph. **37**: 1044, 1938.
67. Schlesinger, E. R., and Mitchell, W. L., Jr.: Sulfanilamide Eruption. A Study of Patients With the Morbilliform Rash and of Their Subsequent Reactions, Am. J. Dis. Child. **56**: 1256, 1938.
68. Sugg, E. S.: Acquired Sensitivity to Cinchophen, Am. J. M. Sc. **135**: 473, 1938.
69. Pautrier, L. M., and Roederer, J.: Aurides licheniennes verruqueuses en nodules isolés et en placards végétants, Bull. Soc. franç de dermat. et syph. **45**: 139, 1938.
70. Schwatt, H., and Rest, A.: The Value of the Patch Test in Gold Therapy, Tubercle **18**: 400, 1937.
71. Tanenbaum, S., Joyner, A. L., Speed, J. A., and Bremer, K. N.: The Use of Staphylococcal Toxoid in the Treatment of 100 Cases of Acne Vulgaris, J. ALLERGY **9**: 241, 1938.
72. Frank, S. B.: Formolized Herpes Virus Therapy and the Neutralizing Substance in Herpes Simplex, J. Invest. Dermat. **1**: 267, 1938.
73. Grace, A. W., and Suskind, R. H.: The Use of Standardized Mouse-Brain Antigen for the Performance of the Frei Test for Lymphogranuloma Inguinale, J. A. M. A. **107**: 1359, 1936.
74. Reider, R. F., and Canizares, O.: Evaluation of the Frei Test With Mouse Brain Antigen: Comparison With Human Antigen, Arch. Dermat. & Syph. **38**: 930, 1938.

75. Binkley, G. W., and Love, W. R., With the Collaboration of Schwartz, W. F., Hitch, J. M., Jr., and Margard, G. A.: Mouse Brain Lymphogranuloma Venereum Antigen: Clinical Experience at Cleveland City Hospital, Arch. Dermat. & Syph. **38**: 383, 1938.
76. Gastinel, P., Pulvenis, R., and Collart, P. A.: A propos de l'immunité syphilitique. Du comportement des lapins traités tardivement, vis-à-vis de la réinoculation, Compt. rend. Soc. de biol **128**: 739, 1938.
77. Tani, T., and Aikawa, S.: Das Wesen der Syphilisimmunität. IV. Ueber die Pathogenese der symptomlosen Reinfektion, Jap. J. Exper. Med. **15**: 303, 1937.
78. Chesney, A. M.: Immunity in Syphilis, Baltimore, 1927, Williams and Wilkins, Co.
79. Chesney, A. M., Woods, A. C., and Campbell, A. D.: Observations on the Relation of the Eye to Immunity in Experimental Syphilis, J. Exper. Med. **69**: 163, 1939.
80. Lewis, G. N., MacKee, G. M., and Hopper, M. E.: The Trichophytin Test: Its Value as a Diagnostic Aid, Arch. Dermat. & Syph. **38**: 713, 1938.
81. Sabin, F. R.: Cellular Reactions to Tuberculo-Proteins Compared With the Reaction to Tuberculo-Lipids, J. Exper. Med. **68**: 837, 1938.
82. Sabin, F. R., and Joyner, A. L.: Cellular Reactions to Defatted Tubercle Bacilli and Their Products, J. Exper. Med. **68**: 853, 1938.
83. Jadassohn, W., Schaaf, F., and Wohler, G.: Analyses of Composite Antigens by the Schultz-Dale Technic: Further Experimental Analyses of Trichophytins, J. Immunol. **32**: 203, 1937.
Jadassohn, W., Riedmüller, L., Schaaf, F., and Zürcher, W.: Schultz-Dale Experiments With Tuberculin Preparations, Schweiz. med. Wchnschr. **67**: 77, 1937.
84. Cooper, H. J., and Cohn, M. L.: Tuberculoprotein, J. A. M. A. **112**: 403, 1939.
85. Birkhaug, K.: Allergy and Immunity (Iathergy) in Experimental Tuberculosis. I. Dispersion of Tubercle Bacilli in the Normal Allergic and Anergic (Desensitized) Guinea Pig, Acta tuberc. Scandinav. **11**: 25, 1937. II. Statistical Interpretation of the Degree of Tuberculosis in Superinfected Allergic and Desensitized Anergic Guinea Pigs, Acta tuberc. Scandinav. **11**: 199, 1937.
86. Willis, H. S., and Woodruff, C. E.: Allergy and Desensitization in Tuberculosis, J. Clin. Investigation **16**: 899, 1937.
87. McCarter, J., Getz, H. R., and Stiehm, R. H.: A Comparison of Intracutaneous Reactions in Man to the Purified Protein Derivatives of Several Species of Acid-Fast Bacteria, Am. J. M. Sc. **195**: 479, 1938.
88. Vollmer, H., and Goldberger, E. W.: Comparative Study of the Tuberculin Patch Test and the Mantoux Intracutaneous Test, Am. J. Dis. Child. **56**: 584, 1938.

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., AND THEODORE B. BERNSTEIN, M.D., CHICAGO

Ragweed Hay Fever: The Effect of Dosage in Treatment of 314 Cases. Dundy, H. D., Levin, L., and Markow, H.: J. Lab. & Clin. Med. **24**: 583, 1939.

The results of specific treatment over a five-year period in a group of 314 ragweed sensitive hay fever patients were analyzed. The factors studied as to their influence upon the results of treatment included (1) sex, (2) method of treatment (preseasonal or perennial), (3) dosage, (4) type of pollen extract used, (5) route of treatment (subcutaneous or intradermal), and (6) degree of sensitiveness of patient as revealed by intracutaneous testing. It was found that sex, route of administration, type of extract (whether prepared from whole ragweed or defatted ragweed), and degree of skin sensitiveness did not influence the results. Of the 314 patients, 84 per cent had satisfactory results, consisting of 5 per cent perfect results and 79 per cent good results. A poor result was obtained in the remaining 16 per cent.

The two factors that bore a relationship to the results obtained were dosage and method of treatment. With increasing maximum dosage, the percentage of satisfactory results increased.

MAXIMUM DOSE FOR SEASON	NO. CASES	PER CENT PERFECT	PER CENT GOOD	PER CENT POOR
0.01 mg. N/c.c.	35	0	62.9	37.1
0.05 mg. N/c.c.	105	2.9	76.1	21.7
0.1 mg. N/c.c.	113	3.5	86.8	9.7
over 0.1 mg. N/c.c.	61	14.8	78.6	6.6

The perennially treated cases showed a greater percentage of satisfactory results than the cases under preseasonal treatment. The authors state the apparent superiority of the perennially treated over the preseasonally treated cases is primarily one of high dosage, as the perennial cases were in the main in the high dose group. Low dosage in the perennial form of treatment yields poor results.

The Incidence of Major Allergic Diseases in Colorado Springs. Service, W. D.: J. A. M. A. **112**: 2034, 1939.

The city of Colorado Springs, Colo., with a population of 35,000, was divided into five economic districts of equal population, and a survey of 200 families in each district was started, relative to the incidence of the major allergic diseases. The diseases considered were hay fever, asthma, eczema, migraine, urticaria, and gastrointestinal allergy. The symptoms were of such severity that all the persons reporting major allergy had found it necessary to seek medical relief. Of the 1,000 families investigated, 505, or 50.5 per cent, had one or more members who

evidenced major allergic manifestations. Of the 3,141 persons interviewed, 711, or 22.6 per cent, presented 842 major allergic manifestations, approximately 16 per cent showing more than one.

Incidence of Major Allergies in 3,141 Individuals (1,000 Families)

	NO.	PER CENT		NO.	PER CENT
Hay fever	316	10.06	Eczema	91	2.9
Asthma	114	3.6	Urticaria	103	3.2
Migraine	116	3.7	G. I. Allergy	106	3.3

The cases are also analyzed as to age, duration, and age at onset.

Of the 711 major allergic subjects, 35.7 per cent gave a family history of major allergy; of the nonallergic subjects only 9.3 per cent had such a history.

Studies on the Chemistry and Immunology of Ragweed Pollen Proteins Hecht, R., Rappaport, B. Z., and Welker, W. H.: Proc. Soc. Exper. Biol. & Med. **39**: 588, 1938

Ragweed extract was separated into two portions. One fraction was that precipitated from solution at a pH. of 3.8 to 4.2 at 60° C. by various buffers. The properties of this fraction are those associated with the properties of the larger protein molecules, i.e., relative ease of precipitation, quantitative absorption with aluminum cream, very little diffusibility through a permeable membrane, and marked viscosity. The second fraction was the filtrate remaining after precipitation of the first fraction. It exhibited the properties of the smaller protein molecules, such as difficulty of precipitation, moderate diffusion through collodion membranes, less viscosity of the solution. It was found that the first fraction is responsible for the precipitin reaction with pollen antiserum. Precipitin experiments done with the filtrate (second fraction) were either negative or diminished. The filtrate contained the skin reactive proteins of the extract, as it was found that the filtrate gave practically undiminished skin tests. Twelve ragweed sensitive patients treated with the filtrate showed no relief. In a few patients treated with filtrate to which had been added gelatin, some evidence of success was obtained.

The Use of Urethane in Symptomatic Treatment of Bronchial Asthma. Farmer, L.: J. Lab. & Clin. Med. **24**: 453, 1939.

Ethyl Urethane ($C_2H_5O.CO.NH_2$) given to sensitized guinea pigs prior to the shocking injection of antigen led to survival of 15 of 30 animals. In the controls, only 4 of 25 guinea pigs survived. Urethane used in vitro was found to inhibit the contraction of sensitized uterine strip which follows contact of the muscle with antigen. The author used urethane to produce symptomatic relief in a small group of cases of bronchial asthma. Dosage used was 1 to 2 gm. dissolved in water and given orally. Not more than 4 gm. were given a day and treatment was not continued longer than four to five days in succession. Satisfactory alleviation action was obtained in 14 of 30 patients. The relief set in after fifteen to thirty minutes and lasted several days. No untoward effects were noted. It is advisable to give urethane before full development of the attack and in some instances to use 1.0 gm. three times daily over a period of three to four days.

Inhalation Therapy of Bronchial Asthma. Graeser, J. B.: J. A. M. A. **112**: 1223, 1939.

The object of the author's study was to determine the most suitable dilution of epinephrine to use in treating bronchial asthma by inhalation, and to make

comparisons between the use of a 1:100 solution of epinephrine and that of other drugs. Eighteen chronic sufferers from asthma used the epinephrine solutions in a hand atomizer with a rubber bulb. The solution found to be the most effective in producing either excellent or moderate results was a 1:100 dilution of epinephrine. With the 1:50 dilution, more frequent reports of systemic symptoms, such as headache, tremor, or palpitation were reported, and without appreciably better relief of the asthmatic symptoms. The 1:100 solution is definitely more suitable under average conditions than the more dilute solutions. The addition of a 1:1000 solution of posterior pituitary solution to 1:100 epinephrine resulted in no appreciable enhancement of relief. A 10 per cent ephedrine sulfate solution and a 5 per cent neosynephrin caused no beneficial results. Relief of asthmatic symptoms was also obtained with a 1 per cent solution of cocaine, but the preparation was less efficient than the 1:100 epinephrine solution.

Local and Systemic Effects From Inhalation of Strong Solutions of Epinephrine. Galgiani, J. V., Proescher, F., Dock, W., and Tainter, M. L.: J. A. M. A. **112**: 1929, 1939.

The authors determined, by weighing epinephrine vaporizers before and after use, that not more than 0.08 mg. of epinephrine is received into the mouth after ten inhalations. Previous investigators had found that only about 3 per cent of the inhaled vapor reaches the lungs, the greater part of the material being deposited upon the pharynx, larynx, and trachea. In 12 asthmatic patients and 4 normal subjects, no changes in blood pressure or pulse rate were observed following inhalation of 1 per cent epinephrine vapor. Cats whose respiratory tracts were divided into three parts, namely, the mouth and nasopharynx, the trachea, and the bronchial airways, had epinephrine solution applied to these regions. No changes in pulse rate or blood pressure were noted following applications to the mucosa above the tracheal bifurcations. Epinephrine instillation to the bronchial mucosa produced characteristic pressor effects. Since clinically the amount of epinephrine reaching the bronchi is very small, the experiments indicate the antiasthmatic effect of the inhaled epinephrine is due to its direct local action upon the bronchial mucosa or musculature.

To determine the local effect of epinephrine upon the tissue of the upper airways, 10 cats and 6 rabbits were given the vapor twice daily for a period of one hundred and twenty-one days. In some of these animals there was found a loss of tracheal cilia, desquamation of the tracheal and bronchial epithelium, tracheitis, and bronchitis. None of the 4 control animals sprayed with sodium chloride showed these changes. Similar changes were observed in the trachea of a tuberculous patient similarly treated for forty-eight hours before death. The authors state that the physician should give careful consideration to the possibility of occurrence of local irritative effects from the inhalation of epinephrine.

Dermatology

UNDER THE DIRECTION OF MARIAN SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

Studies on the Sensitization of Animals With Simple Chemical Substances. VI. Studies on the Sensitization of Guinea Pigs to Poison Ivy. Landsteiner, K., and Chase, M. W.: J. Exper. Med. **69**: 767, 1939.

The isolation of an island of skin in the guinea pig by means of an oval incision through the skin was found not to inhibit the generalization of sensitivity to poison ivy when the sensitizing application was made to the island. When, however, the

incision extended through the underlying thin muscular layer (thus interrupting the lymphatic drainage from the island), general and local sensitization did not result from the application of poison ivy extract to the isolated skin area. General sensitization is thus not dependent upon a maintenance of the continuity of the skin. On the other hand, it seems likely from these experiments that the continuity of lymph channels is of considerable importance in the spread of cutaneous sensitivity.

The incision through the lymph channels was found to inhibit anaphylactic sensitization to horse serum only when small amounts of the allergen were injected into the isolated island of skin.

Protective Antibodies in the Serum of Syphilitic Rabbits. Turner, T. B.: J. Exper. Med. **69**: 867, 1939.

An emulsion containing virulent *Treponema pallidum* was mixed with normal rabbit serum and with serum from rabbits which had been infected previously with a homologous strain of *T. pallidum.* The mixtures were incubated at 37° C. for six hours. Typical syphilitic lesions resulted from the intracutaneous injection of the mixture of normal serum and emulsion of *T. pallidum.* On the other hand, the injection of the emulsion plus the serum of the previously infected (immune) animal resulted either in no lesions at all or in lesions which were smaller than those produced by the injection of the normal serum mixture. Furthermore, when lesions appeared following the injection of the mixture of spirochetes and immune serum, the incubation period was shorter than usual. It was possible to demonstrate the protective action of the immune serum by the inoculation of both immune serum-spirochete emulsion and normal serum-spirochete emulsion simultaneously into a given animal. The protective action of the immune serum was lessened by heating to 56° C.

Early Acute Arsenical Erythemas. A Study of Eleven Cases of the "Erythema of the Ninth Day" of Milian. Canizares, O., and Thomas, E. W.: Arch. Dermat. & Syph. **39**: 867, 1939.

The patients reported represented about 3 per cent of the patients treated for the first time with arsenical drugs in the wards of the Bellevue Hospital during the two years covered by this study. The average duration of the reaction was five to six days. Sore throat was frequent but not invariable. No common factor of dosage, type of arsenical used, or spacing of treatments could be discovered. Three patients, whose reaction appeared after their second injection with an arsenical, were given a third injection during the reaction, with no serious exacerbation of symptoms. For the most part, however, injections were interrupted until the reaction had subsided.

In 3 cases there was a purpura in addition to an erythematous skin eruption. Further therapy was attempted in 2 of these cases, with no recurrence of the purpura. In 8 cases patch and intradermal tests, performed during the reaction, were entirely negative. In 4 cases passive transference (Prausnitz-Küstner) was negative. Most of the patients subsequently were given injections of arsenicals, although nitritoid and gastrointestinal reactions were fairly common.

Sensitivity to Arsenical Drugs. Report of an Unusual Case Exhibiting Sensitivity to Both Trivalent and Pentavalent Arsenic. Golz, H. H.: Am. J. Syph. Gonor. & Ven. Dis. **23**: 344, 1939.

The patient reported the development of a severe exfoliative dermatitis following the sixth injection of neoarsphenamine. Eight months later, after recovery from the exfoliative dermatitis and after treatment with malaria followed by a

series of injections of bismuth salicylate, she was given her first injection of tryparsamide (2 gm.). A severe exfoliative dermatitis ensued, the first symptoms appearing four hours after the injection.

After recovery from the second attack of exfoliative dermatitis, patch tests were performed with old arsphenamine, neoarsphenamine, silver arsphenamine, sulfarsphenamine, mapharsen, and tryparsamide. All were positive. The reaction to tryparsamide, which was the least severe of the reactions, presented moderate edema, itching, and inflammation, but no vesiculation.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND MAX HARTEN, M.D., BROOKLYN

Sensitization and Antibody Formation in Monkeys Injected With Tubercle Bacilli in Paraffin Oil. Casals, J., and Freund, J.: J. Immunol. 36: 399, 1939.

It has been reported that the *Macacus rhesus* monkey is lacking in the capacity to develop cutaneous sensitization to tuberculin. The addition of paraffin to heat-killed tubercle bacilli promotes sensitization of the guinea pig and the rabbit to tuberculin. The present study was undertaken to determine whether tubercle bacilli in paraffin oil can effectively sensitize the *rhesus* monkey.

Tests for tuberculin sensitiveness were made by the intracutaneous injection of 0.2 c.c. of a 20 per cent dilution of old tuberculin. The reactions were read on each of the first three days after testing. The reaction was considered negative if it persisted less than forty-eight hours. Tubercle bacilli were used as antigen in the titration of complement-fixing antibodies.

Three animals received, at varying intervals, multiple subcutaneous injections of 1.0 mg. of heat-killed tubercle bacilli suspended in saline solution. In one animal neither antibody function nor tuberculin sensitiveness could be demonstrated. The other 2 animals showed transient tuberculin sensitivity, which persisted from two to six weeks. Antibody formation, demonstrable in these animals, persisted from seven to twenty-one weeks after the last injection of heat-killed tubercle bacilli. The highest titer observed was 1:20.

Another series of 4 monkeys received multiple subcutaneous injections of 1 mg. of heat-killed tubercle bacilli in 0.5 c.c. of paraffin oil. These animals all exhibited intense tuberculin reactions with superficial necrosis. Antibodies appeared in the serum in titers up to 1:80. Tuberculosis, not uncommon in monkeys, was looked for in these animals. Only sparsely scattered subpleural nodules were found, while cut surfaces of the lung, spleen, liver, and kidneys presented no evidence of tuberculosis.

The authors conclude that antibody formation and weak sensitization to tuberculin can be produced in the *Macacus rhesus* monkey by heat-killed tubercle bacilli. However, the suspension of this antigen in paraffin oil induces abundant antibody formation as well as intense and lasting sensitization.

The Production in Experimental Animals of Antibodies to Short-Ragweed Pollen (Precipitation, Complement-Fixation, and Anaphylaxis). Eagle, H., Arbesman, C. E., and Winkenwerder, W.: J. Immunol. 36: 425, 1939.

Although extracts of ragweed pollen have been found by most workers to be antigenic in rabbits and guinea pigs, the antibody response has usually been irregular and weak. The authors, therefore, decided to reinvestigate the immunization of experimental animals with this antigen.

Rabbits were injected subcutaneously, intra-abdominally, intracutaneously, and intravenously with a suspension of ground short ragweed pollen, with saline extracts of ground pollen, and with buffered alkaline extracts of defatted whole pollen. The immunizing injections were given three times weekly over a period varying from thirty to thirty-nine days. The total amount of pollen extractives injected varied between 0.3 and 0.95 gm. The antibody response was determined by precipitation tests, by complement-fixation, and by the estimation of antibody protein. All rabbits, regardless of the route of sensitization or type of extract used, regularly developed precipitins and complement-fixing antibodies in high titer. One-eighth to 0.33 gm. of extracted pollen derivative containing approximately 30 mg. of nitrogen was found to suffice for sensitization. The total amount of antibody protein, determined in 10 different rabbit sera, ranged between 40 and 140 mg. per 100 c.c. of serum.

Forty-seven of 79 guinea pigs passively sensitized by the intra-abdominal injection of from 1 to 4 c.c. of these rabbit antisera and shocked from twenty-four to forty-eight hours later by the intracardiac injection of from 0.5 to 1.5 c.c. (0.5 to 2 mg. nitrogen) of ragweed pollen extract, died in characteristic anaphylactic shock. Eighteen of the remaining 32 animals developed definite, but not fatal, anaphylaxis.

Forty-eight guinea pigs, actively sensitized by a single intra-abdominal injection of from 0.25 to 4 c.c. either of Coca extract of ragweed pollen or of ball mill extract, were shocked nineteen to twenty-six days later by the intracardiac injection of from 1.0 to 1.5 c.c. of the ragweed extract. Twenty-four of the 48 animals died in acute characteristic anaphylactic shock within five minutes. Nineteen of the remaining animals exhibited definite, but not fatal, anaphylaxis. Essentially similar results were obtained with each of the two extracts used. Three of 4 sensitized guinea pigs, tested by the Dale technique, gave positive results.

On the Serological Specificity of Peptides. III. Landsteiner K., and van der Scheer, J.: J. Exper. Med. **69:** 705, 1939.

In the present communication the authors have investigated the serologic behavior of synthetic substances of somewhat complex structure, i. e., immune sera to pentapeptides and peptide amides. The peptides used for the preparation of azoantigens were tetraglycl-glycine, tetraglycl-leucine, d, l-diglycl-leucyl-glycyl-glycine, and trileucyl-glycl-glycine.

Rabbits were sensitized by from two to four courses of six daily intravenous injections of 5 mg. of horse azoprotein suspension, with rest intervals of one week between courses of injections. The animals were bled on the seventh day following the last injection. Precipitin and inhibition tests were carried out with azoantigens prepared with chicken serum.

Although all the four pentapeptides studied contained only glycyl and leucyl residues, they were distinct in their precipitin reactions when tested with the various antigens. Replacement of even one of the five glycines by leucine resulted in a noticeable alteration in serologic properties. A pronounced serologic change was also brought about by the conversion of peptides into amides or upon esterification of peptides. No indication of the presence in the immune sera of special antibodies for portions of the peptide molecule was observed. The antibodies produced by pentapeptides appeared to be specific for the entire pentapeptide. It thus appears that antibodies may be formed which are specific for peptide chains consisting of five amino acid residues.

Placental Transmission of Hypersensitiveness to Ascaris Lumbricoides Actively Induced in the Pregnant Woman. Zohn, B.: Am. J. Dis. Child. **57:** 1067, 1939.

A study was undertaken to determine whether sensitivity to *Ascaris lumbricoides*, actively induced in women during pregnancy, could be transferred passively to the offspring.

Twelve nonatopic women, in the third trimester of pregnancy, received from three to nine weekly intracutaneous injections of 0.05 c.c. of ascaris extract (0.1 mg. N per c.c.). Preliminary intracutaneous tests with this extract were negative. At the termination of pregnancy, blood, drawn from both the mother and from the fetal cord, was studied by the Prausnitz-Küstner method for the presence of reagins. One week was allowed to elapse between the time of cutaneous sensitization of nonatopic substitutes and that of testing.

Reagins for ascaris were demonstrated in 9 of the 11 mothers from whom blood was obtained. Reagins could not, however, be demonstrated in serum from the fetal cord in a single instance.

The author concludes that intrauterine sensitization of the human fetus is not easily accomplished and that sensitization of the pregnant woman does not affect the fetus.

The Thyroid Gland and Allergy. Experimental Studies on the Dependence of the Allergic Reaction on the Functional State of the Thyroid Gland. Eickhoff, W.: Virchows Arch. f. path. Anat. 303: 481, 1939.

The author reports the results of his studies on the relationship of the thyroid gland to anaphylaxis.

Rabbits were sensitized by five subcutaneous injections of 2 c.c. of swine serum at five-day intervals. The minimum lethal anaphylactic dose, the average intensity of the Arthus reaction, the precipitin formation, and the complement fixation were determined. The effect of resection of the cervical sympathetic and vagus nerves, of thyroidectomy, and of the administration of thyroid on sensitization and anaphylaxis was then noted. The effect of sensitization on the histologic picture of the thyroid was also observed.

Histologic examination of the thyroid gland of 18 normal animals indicated that the gland in the rabbit was normally in a quiescent state, with an active follicle occasionally present on the periphery. Following sensitization there resulted a marked activity of the central follicles of the gland, similar to that observed in the thyroid gland of rabbits artificially stimulated by the administration of thyroid extract. Similar results were reported in sensitized guinea pigs. Resection of the cervical sympathetic nerves prior to sensitization prevented the activation of the thyroid gland. After a unilateral vagotomy, performed prior to, or subsequent to, sensitization, a normal quiescent thyroid was observed. Thyroidectomy, performed prior to sensitization, had a marked inhibitory effect on precipitin formation and on the production of the Arthus phenomenon. In thyroidectomized animals the administration of extract of whole thyroid gland increased sensitization to the degree observed in nonthyroidectomized controls.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Anaphylactogenic Properties of Certain Cereal Foods and Breadstuffs. Ratner, B., and Gruehl, H. L.: Am. J. Dis. Child. 57: 739, 1939.

Guinea pigs were sensitized intraperitoneally with a $\frac{N}{100}$ potassium hydroxide extract of each of the common grains. Three weeks later similar alkaline extracts of common cereal products in which the corresponding grain was used were injected intravenously in an attempt to induce anaphylactic shock.

Using this technique, it was shown that certain grain products were so altered by moist heat in the course of their preparation or manufacture that their anaphylactic properties were diminished or lost.

Evidence is brought forward which indicates that the diminished antigenicity of such products depends on the fact that heat tends to render the antigen insoluble. This change is much less likely to take place in dry heating, as in bread and pastry-making, than it is in moist heating, as in double boiler cooking of hot cereals, the cooking of spaghetti, and in the manufacture of some multiple precooked dry cereals. This study again brings out an observation of Wells and Osborne, namely, that wheat and rye have a closely related common antigen (gliadin). Animals sensitized to wheat were shocked by rye extract and vice versa.

The authors conclude on the basis of these animal experiments that elimination diet lists should be revised to include allergenically denatured cereal products such as those he describes.

Intelligence Rating and Emotional Pattern of Allergic Children. Chobot, R., Spadavecchia, R., and De Sanctis, R. M.: Am. J. Dis. Child. **57**: 831, 1939.

In a study of 169 children taken from an allergy clinic the authors conclude that allergic children are neither advanced nor retarded mentally as a group and that the distribution curve of their intelligence scores follows the normal. They showed no tendency to proficiency or deficiency in any particular field. Data on 100,000 New York public school children was used for the comparison.

Twenty allergic girls and 45 allergic boys were then compared with 2,000 school children in regard to emotional pattern and adjustability, using the Pintner Personality Outline. The conclusion was reached that, although the allergic children as a group showed a slight tendency to submission and introversion, they were better adjusted to their environment than the average child. In addition, allergic girls were more stable emotionally than normal girls.

It comes as somewhat of a surprise, therefore, that the authors report that a further test (the Pintner Pupils' Portrait Questionnaire) showed normal boys and girls to be better adjusted to school, teacher, pupils, family, and self than the allergic group. They feel this is not a contradiction.

Some Cases of Cows' Milk Idiosyncrasy. Sydow, G.: Acta Paediat. **23**: 384, 1938.

After reviewing 4 cases of cows' milk sensitivity in infants from the Gothenburg's Children's Hospital, and 12 additional cases gathered from the literature, Sydow feels that two general types are apparent. In one there is a firm constitutional foundation and family history of allergy, and the manifestation is asthma, eczema, or both. Sensitization is persistent and desensitization is difficult or impossible. The other group shows no particular constitutional predisposition and no family history of allergy, and the manifestation of sensitivity is chiefly by the gastrointestinal tract; desensitization or spontaneous loss of sensitivity is common.

Problems of So-Called Infantile Eczema. III. Seborrheic Dermatitis. General Survey. Tachau, P.: Acta dermat. venereol. **20**: 232, 1939.

Seborrheic dermatitis is common in infancy and childhood and is characterized by circular red lesions with sharp borders, and a tendency to secondary eczematization. It is much less common on the body. Lerner's erythroderma desquamation is a special type of seborrheic dermatitis found early in life.

Tachau is more hopeful of influencing eczema by general dietary measures than by specific elimination. He is convinced that external irritation is a very important factor. A nonspecific diet high in fruit and vegetables and low in fat is suggested in atopic dermatitis.

Controlled Insulin Shock Treatment of Asthmatic Children. Vollmer, H.: Arch. Pediat. **56**: 223, 1939.

In treating a schizophrenic patient by insulin shock therapy, Sakel noticed that the patient's asthma was markedly improved. Accordingly, this mode of treatment was tried in asthmatics, and remarkable results were reported by Wegierko in adults. Vollmer applied it to 7 asthmatic children and all were benefited, at least temporarily. Treatments were 15 to 25 in number over a period of one and a half to three months. Up to 40 units of insulin were given, but in no instance was the hypoglycemic reaction permitted to become severe. Symptoms were carefully controlled with glucose by mouth or, if necessary, by vein. The effect is ascribed to the secondary endogenous formation of adrenalin in the patient and to a possible compensatory hyperfunction of the adrenal gland. It is suggested that in chronic asthma adrenalin should be replaced by insulin.

The Metabolism Relationship Between Exudative Diathesis and Alimentary Intoxication. Goldmann, F.: Ann. paediat. **152**: 160, 1939.

Goldmann points out that sodium retention, as indicated by the urinary sodium chloride quotient, occurs in such varied conditions as generalized eczema, alimentary intoxication, and prematurity. He conceives this is associated with a "transmineralization" into the tissues, and is manifested by a tendency to edema. It depends on altered cell permeability. Azotemia, said to be common to all these conditions, is possibly a cause of the disturbed permeability. Whether the cell membrane or cell protoplasm is primarily concerned in these electrolyte changes cannot be decided at the present time.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Allergic Rhinitis. Jones, E. H.: South. M. J. **32**: 647, 1939.

In his discussion of allergic rhinitis, Jones states that it is difficult to differentiate clearly perennial hay fever and allergic rhinitis. Those cases in which the primary symptoms are sneezing and rhinorrhea and in which the nasal mucosa is pale were considered as perennial hay fever. The cases with a red nasal mucosa were considered as allergic rhinitis. Is there a justification for making this distinction between a pale and a red mucosa? Considering all cases of allergy in the nose as nasal allergy, there is a definite variation in the type of mucosa observed, namely, normal appearance, slightly pale, markedly pale or edematous, or red. Nasal polyps are usually present with the pale mucosa. There appears to be no reason, therefore, for the introduction of additional terminology.

Cold Vaccines: An Evaluation Based on a Controlled Study. Diehl, H. S., Baker, A. B. and Cowan, D. W.: J. A. M. A. **111**: 1168, 1938.

At the University of Minnesota, Diehl and his co-workers conducted a three-year study of cold vaccines used on students. Nasal allergy and sinus infections were excluded. The conclusions may be summarized as follows: The group receiving vaccine subcutaneously experienced an average of 25 per cent fewer colds per person than did the control group. The difference is considered of no importance, however, because a reduction of 25 per cent is not sufficiently great to justify the time and expense in giving the treatment. The group who received a polyvalent

vaccine orally experienced just as many colds as the control group. Although the data presented are not conclusive, there is no evidence in this study either that the vaccines reduce the complications of colds or that the condition of the nose and throat is related to the frequency of colds in the cold-susceptible group.

A Controlled Study of "Cold Vaccines." Hauser, I. J. and Hauser, M. J.: Arch. Otolaryng. **29:** 704, 1939.

The controlled study of cold vaccines by Hauser and Hauser was conducted on a series of 369 students at the University of Michigan. The following conclusions were drawn: Over 66 per cent of subjects who received placebos stated that they had fewer colds than during the year preceding the experiment. Of the persons who received vaccine intradermally, over 64 per cent considered themselves similarly improved. Of those who received the vaccine subcutaneously, 80 per cent reported fewer colds than the preceding year. Although the proportion of subjects reporting improvement was greatest in the group in which the vaccine was given subcutaneously, the percentage of difference between the three groups was considered within the limits of possible error.

Manifestations of Allergy in the Ear. Jones, M. F.: Ann. Otol. Rhin. & Laryng. **47:** 910, 1938.

Jones discusses the occurrence of an allergic type of otitis media. In one instance a child was found sensitive to chocolate, nuts, and wheat. The attack was induced by the ingestion of nuts. In a case of chronic allergic labyrinthitis the symptoms disappeared upon the elimination of milk.

Corneal Reactions to Weed Pollen. Annenberg, A. R.: Am. J. Ophth. **3:** 1265, 1938.

Annenberg reports 6 patients in whom corneal lesions followed the cutting of weeds. Five of the patients complained of pain, redness, itching, and sensation of a foreign body in the eyes. The palpebral and bulbar conjunctivae showed redness but no corneal involvement. From two to four days later, however, grayish areas of infiltration appeared in the cornea. These reactions lasted several days. Pigweed was found to be the offending factor. One of the patients had other manifestations of allergy. Treatment consisted of the daily injection of foreign protein.

Correspondence

Portland, Me.,
April 24, 1939.

The Editor,
JOURNAL OF ALLERGY.

Dear Sir:

In reply to a request from the librarian of the Royal Australasian College for a reprint concerning ragweed pollen in Maine, I inquired whether ragweed was present in Australia also and when it was introduced. My letter was referred to the Division of Plant Industry of the Council for Scientific and Industrial Research. The following information was received, which, I thought, may be of general interest to readers of the JOURNAL.

Ragweed is recorded for Victoria as naturalized in 1912 and as occurring in Wimmera in 1890. It is evident that the weed was introduced about fifty years or so ago in Victoria, and it gradually spread until it was more or less generally recognized by 1912. Since then it has, of course, spread further in that state. It is recorded from South Australia here and there in the Mount Lofty ranges.

How it was introduced is uncertain; probably it came in fodder or in seed.

The perennial ragweed *A. psilostachya*, from the western United States, is found in cultivated land at Berri and Naracorte in South Australia.

Ragweed is a proclaimed weed for New South Wales and possibly other Australian states.

CHARLES B. SYLVESTER